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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

OCTOBER 1948

VENOUS THROMBOSIS AND PULMONARY EMBOLISM*

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INTEREST has become more universal in the problem of venous thrombosis and pulmonary embolism in the past decade than appears to have been evident in any previous era. Although there is still much to be learned about this common complication of illness, injury, parturition and surgery, we believe some progress has been made. In spite of the various established aids in the prevention of thrombosis and in the treatment of the disease in its non-fatal form, the fact remains that a considerable number of people still die from this cause. The literature is voluminous concerning the good results obtained by the treatment of patients who develop thrombosis of the leg veins and sublethal embolic processes. Few reports have been made however that parallel the incidence of quickly fatal massive pulmonary embolism occurring in the same institution during the period of time covered by the study. Obser-

* Given March 5, 1948 before the Section on Surgery of The New York Academy of Medicine.

vations on the preventive methods tried are also open to criticism since one can, by comparison with a previous or control group of patients, obtain only an estimate of the values rather than the accurate determinations often possible in the study of other problems. Since the above statements apply to our own publications on the subject, as well as those of others, it is obvious that we do not have the final solution. We believe, however, if all interested in this field will continue to view the situation in a critical manner, that better and probably simpler methods of management will be evolved.

We are aware that in a group of patients of the same sex, age, physical condition, afflicted with the same disease and treated in the same manner, there will be only a certain percentage who will develop thrombosis of the leg veins with or without pulmonary involvement. It seems that there should be evolved simple criteria to indicate which patients would be likely to have such complications. It is true that in determining the prothrombin level in a large number of patients, we find a few with a slightly lowered and a few with a slightly elevated prothrombin time. On the whole, however, the present methods of measurement would fail to give us sufficient evidence to warrant extra precautions in most cases. Since at this time we have no reliable laboratory studies to help us predict the outcome in the majority of patients, we must use the clinical data pertaining to the subject that is available. Gradually there is being collected clinical material that will in time make it possible to estimate the risk of thrombosis and embolism in given pathologic states for various age and sex groups. It is quite probable that the risk will prove to be lower in certain geographical locations than in others. It is known that thrombosis occurs less frequently during the summer months than during the winter in New England.

Cardiac patients as well as those with other medical diseases requiring quiet, sedation, bed rest in a sitting position, etc., are common victims of thrombosis and embolism.

Extensive malignancy, involving the abdominal viscera particularly, tends to lead to these complications even in the inoperable phase. It is not unusual to have fatal embolism occur during the otherwise normal convalescence following operative procedures on malignancy of the colon and stomach.

Acute intra-abdominal infections, such as appendiceal abscess, are more prone to be associated with thrombosis and embolism than infec-

tions elsewhere. Since acute small bowel obstruction gives a high incidence of this syndrome, it may well be that ileus or abdominal distention is more important in contributing to these complications than the infectious process itself. It has appeared obvious that depleted patients from any cause whatever are more subject to thrombosis than are those in good general condition.

Furthermore, we believe that much can be accomplished in lowering the incidence of thrombosis and embolism by utilization of the many pre- and postoperative general measures now commonly known. Elimination of stasis in the leg veins by bandage and posture, muscular activity in bed and early walking are all helpful and generally practiced.

Certain definite facts concerning the development of thrombosis are now well established.[1] These are beginning to be recognized generally, but series of cases treated either prophylactically or therapeutically without consideration of these known predisposing factors are still being reported. The age of the patient is probably the one important factor most commonly ignored. Although it is possible to show that age in years can be used as a general rule, it remains for consideration that some patients of less than 50 years of age may be more deteriorated than others of 70. Actually, it appears that infirmity with its influence on muscular activity plays an important role. *Trauma involving the lower extremities* is likewise a well-known predisposing factor to thromboses of the veins. This may be comparatively minor in character such as a contusion or abrasion. Burns involving the lower limbs are likewise conducive to this complication. The frequent development of thrombosis following thigh amputations and fractures of the leg and hip region is now accepted.

In viewing this subject as a whole, it is obvious that we have two distinct methods of attack. These are treatment of the condition after evidence of its existence is apparent, or specific prophylactic measures that may prevent thrombosis. Aside from the general measures practiced in all patients that can be adapted to them, we have other means at our disposal to diminish the chance of thrombosis. It must be admitted that we cannot utilize many of the aids available in every case. Although prevention of stasis in the leg veins by posture, compression bandages and active or passive exercises can be carried out in a very high percentage of ill or postoperative patients, there are many instances when this cannot be effectively done. We also feel that under given circum-

stances, one form of specific prevention may be more suitable than another.

Our experience now covers a period of 20 years of awareness of the seriousness of the problem. The first decade was devoted to general measures of prevention of thrombosis and it appears that by these means, postoperative fatal emboli were reduced from 3 in 1000 to 1 in 800 cases in our clinic.[2] It must be remembered that during this time there was a gradual improvement in the preoperative preparation, operative technique and postoperative care. These measures reduced the operative mortality from other complications as well as those from thromboembolic disease. Slowly at first but with greater impetus during the past decade, attention has been directed to specific methods of prevention and treatment of this syndrome. As the operative mortality from other complications became reduced to such a low point, the sudden exodus from massive embolism became more impressive.

Perhaps enough has been said about the two types of thrombosis of the veins. It seems now that these should be thoroughly understood and accepted. Whether there is a common origin of the thrombus regardless of its type is somewhat irrelevant except from an academic standpoint. It seems doubtful to us that all thromboses are alike in the beginning. The sudden occurrence of pain and swelling in the leg associated with the elevation of temperature and pulse so characteristic of thrombophlebitis defines this form in a distinctive fashion. That a non-inflammatory thrombus should always precede it seems unlikely. In phlebothrombosis, we rarely have adequate evidence of the process until it is well advanced or until a pulmonary infarct has occurred. The legs on examination appear normal in the early stage and there is no noticeable reaction as manifested by a rise in temperature, pulse, and respiration on the clinical chart until an infarct, although often painless, has taken place. It is from this type of bland thrombosis that nearly all of the fatal emboli occur. The lack of inflammatory reaction in the vein is responsible for the clot remaining unattached to the vein wall. If all of the thromboses were immediately inflammatory in type, there would be only rare embolic deaths and these would come from a propagating thrombus at a higher level in the venous system. We have observed all gradations of the disease and it is certain that non-fatal phlebothrombosis will often develop into thrombophlebitis. This may be a gradual process actually requiring weeks of time on occasion.

Frequently, the swelling and pain in the leg characteristic of thrombophlebitis may not appear until long after the first infarct and rarely after femoral vein interruption for phlebothrombosis has been carried out. True phlegmasia alba dolens is now an unusual picture and is seen only in our clinic in patients treated elsewhere for some period of time before coming to us. The prolonged morbidity associated with this disease, so common 10 years ago, is no longer observed. Treatment of the condition in its early stages, whether it is inflammatory or bland in type, has eliminated the prolonged convalescence and sequelae seen in former years.

Up to January 1, 1948, over 2600 patients at the Massachusetts General Hospital have received some form of specific measures for the prevention of or the treatment of the thrombo-embolic syndrome. In this group of cases, there were 12 deaths related to the process toward which the treatment was directed. One can only estimate the number of fatalities in this group of patients if no specific treatment for the complication present or feared had been given. Deaths from pulmonary embolism occur in untreated cases in this hospital still, in spite of our alertness to the possibilities. In some instances, the type of illness or the condition or physical development of the patient seemed to offer a reasonable contraindication to any of the specific remedies available. Others occur in patients under the care of skeptics on the staff regarding the efficacy of the measures usually accepted. There occurred also rare instances of fatal embolism in patients that would ordinarily not be expected to develop such a complication. It seems fair by comparison of past and present experience to assume that the estimated deaths in the treated group would have increased tenfold had specific treatment been withheld. The following statistical analysis of our experience has been useful to us and may be helpful to others in the evaluation of this problem.

Prophylactic Measures

Although our earlier experience was confined to the general prophylactic measures mentioned above and so universally adopted, it will be assumed that such were carried out when feasible in all cases referred to in this presentation regardless of any specific methods used. Prevention of thrombosis, particularly in the veins of the lower extremities by any means whatsoever, is far more important than the treatment of

the condition after it arises. For this reason, we would like to discuss this phase of the question first. Since we have no reliable laboratory data to furnish us with a clue regarding the likelihood of thrombosis in the majority of patients, we must rely on clinical observations. In earlier publications, we have shown that fatal embolism is unusual under the age of thirty. Although rare instances occur, it would seem impractical at the moment to use any of the specific measures to prevent thrombosis that are now known to us. Also, it must be borne in mind that if thrombosis develops in younger patients, the warning signs are much more prone to be sublethal in character than in the aged. For this reason, we believe it is justifiable with few exceptions to use only general measures on patients under the age of 30 and treat to the best of our present ability the complications that arise.

In the middle aged group, we have a large percentage of patients who have no contraindication to the anticoagulants and can in large part be protected from thrombosis by their proper use. It is our feeling that the hazards of this form of treatment have not been sufficiently stressed. It is difficult to put down a simple, easily understood plan that can be utilized by most doctors or by a large percentage of hospitals. The best results have been reported by groups of physicians who have been able to concentrate on the problem without interference. They have had a good working knowledge of the problem as a whole and have had adequate laboratory facilities at their disposal. It is obvious that these drugs cannot be used empirically and that each patient must have complete, careful, and intelligent supervision. It is our feeling that patients in the older age group should more cautiously be given anticoagulants. Our reason for this opinion is based on a rather high percentage of deaths observed in our hospital when heparin or dicumarol was used in patients with arteriosclerosis. The percentages of cerebral hemorrhages in these patients has been too high to warrant its frequent use. Much of this experience was obtained in earlier years than those covered by this report and apply to the use of heparin in the treatment of bacterial endocarditis by the medical service.[3]

We feel that we have unquestionably established the safety and feasibility of interruption of the normal superficial femoral veins in the prophylaxis against thrombosis and embolism. This has not been generally accepted because physicians, who have not had such a procedure done on themselves or on their patients, cannot believe that interrupting

TABLE I—SUMMARY—THROMBO-EMBOLIC DISEASE

Massachusetts General Hospital—1937-1947

	No. of Patients	*Fatalities*
Prophylactic Dicumarol	536	2
Prophylactic Sup. Fem. vein interruption	871	4
Therapeutic Phlebotomy, Thrombectomy, and Fem. vein interruption	1260	6
Total	2667	12 (0.45%)

a large vein in the thigh could be devoid of danger to that extremity. We were skeptical about it ourselves at first but came to realize, after adopting routine bilateral superficial femoral vein interruption in the treatment of thrombosis, that sequelae were negligible on the unthrombosed side. For these reasons, we feel that under proper circumstances and in suitable cases, this procedure is preferable to any other. This is particularly evident in patients who have injuries to the lower extremities where immobilization is necessary or where wounds prevent freedom of muscular activity. Likewise in the depleted, very ill patient with advanced carcinoma or infection and often on the basis of age alone, active exercises cannot be effectively carried out. Even if it were considered safe to use anticoagulant therapy in many of these patients, the duration of the treatment with its constant laboratory control would create a more serious hospital problem than prophylactic superficial femoral vein interruption.

It was possible to demonstrate in a controlled study of two similar groups of patients, of middle age treated by small doses of dicumarol postoperatively, that this drug was effective in reducing the incidence of thrombosis by 80 per cent. We feel that with a more intelligent use of this drug or a substitution of heparin in resistant patients that a further reduction would have been made. We are convinced, however, that indiscriminate use of anticoagulants without laboratory control will lead to fatal complications. One must weigh these possibilities carefully when these potent drugs are used. In both of our fatalities (Table I), following its use, justifiable criticism is obvious.

One patient aged 46 was known to have moderate hypertension. He had a simple partial colectomy with primary anastomosis for a constricting carcinoma of the sigmoid; 200 mg. of dicumarol was given on the first postoperative day and 14 hours later he had a large subarachnoid hemorrhage. The prothrombin time was 20 seconds over a normal of 19 seconds. Massive doses of vitamin K were given with a drop to normal in prothrombin time. Sixteen days later, however, his prothrombin time was 27 over a normal of 18 seconds. Since he continued to bleed intermittently, a carotid artery ligation was recommended and carried out by the neurosurgical service. The patient failed to survive this procedure. It is fair to say that this patient should not have had anticoagulant therapy. Furthermore, it seems doubtful that the 200 mg. dose of dicumarol with its usual delayed action could have influenced the original cerebral hemorrhage within 14 hours after its administration. The slight change in the prothrombin level 24 hours after giving the dicumarol may be within the limits of laboratory error.

The other fatality occurred in an 82 year old man who had a transurethral resection of his prostate. Eight days later, he developed an incarcerated sliding hernia and was operated upon 2 days afterwards. Following this, he received 200 mg. of dicumarol, by error, and 3 days later, 13 days after his prostatic resection, bilateral superficial femoral vein interruption was done as a prophylactic measure. The next day his prothrombin time was 26 over a normal of 18 seconds. The following day, now 15 days after the prostatic procedure, 5 days after herniorrhaphy and dicumarol therapy, and 2 days after femoral vein interruption, he bled massively from the prostatic bed. In spite of vitamin K and blood transfusions, his prothrombin time was not reduced to below 22 seconds. He bled twice more in the next two weeks and his N.P.N. reached 80 mg. per cent. Forty-six days after his initial operation, he had a sudden episode resembling cerebral hemorrhage and succumbed. Unfortunately, no autopsy was obtained. In this case, dicumarol should not have been used and we think that this is the oldest patient to have received this drug in our hospital. It appears that this patient may have been particularly sensitive to the drug.

It is important to observe that no patient receiving dicumarol therapy as a prophylactic measure died of pulmonary embolism. Since the two deaths reported above may well have been due to other causes than the dicumarol therapy, we feel that this drug when properly used

TABLE II

RESPONSE TO 200 MGM. PROPHYLACTIC DICUMAROL
1947—254 Cases

	Good	*Poor*	*Undetermined*	*Total*
Single Dose	78	21	20	119
Multiple Dose	113	20	2	135
Total	191 (75%)	41	22	254

has much to commend it. We have observed another patient with almost fatal bleeding from misuse of dicumarol given elsewhere. This patient of 38 had undergone hysterectomy and had developed thrombophlebitis on the 11th postoperative day. Without laboratory control, the patient was given daily doses of dicumarol totaling 3500 mgs. in a three week period. Her thrombophlebitis had subsided and she was sent home. She was admitted to our hospital within twenty-four hours, bleeding from the nose, kidneys, and into the spinal fluid, and with a hemiplegia thought to be due to hemorrhage. After very heroic treatment with Vitamin K, and whole blood transfusions, her prothrombin time, which on admission was unobtainable because of lack of all clotting ability, was reduced to normal in 48 hours. She was well save for the residual paralysis from the cerebral hemorrhage on discharge 28 days later.

Table II shows the type of response to 200 mg. doses of dicumarol given prophylactically in 254 patients treated in the year 1947. Seventy-eight of these were given only 1 dose, while 113 had multiple doses. It appears that at least 75 per cent of these patients responded satisfactorily to this method of treatment.

Table III reveals the complications we have encountered with the drug, including the patients who developed phlebitis or infarcts in spite of its use. It appears that, even in those patients who show what we consider to be an adequate response to the drug, a few develop phlebitis and infarcts requiring femoral vein interruption. It is quite possible that these patients could have been more vigorously treated. We have increased the initial dose in certain very large individuals and have more

TABLE III

COMPLICATIONS OF PROPHYLACTIC DICUMAROL IN 496 PATIENTS

Massachusetts General Hospital—1945-1947

	With Response	*Without Response*	*? Response*	*Total*
*Minor Bleeding	12	0	0	12
*Major Bleeding	1	0	0	1
**Phlebitis	2	5	4	11
**Infarct	6	0	5	11
Fatal Pulmonary Embolus	0	0	0	0
Deaths from delayed hemorrhage	1	1	0	2

* Requiring Vitamin K or Transfusion.
** Requiring Femoral Vein Interruption.

recently given subsequent doses when the prothrombin time has not indicated a suitable response.

Bleeding from suture lines and the tendency of large dead spaces to fill with blood after the use of dicumarol is to be noted. The typical examples of these are more frequent and copious hemorrhage in primary intestinal anastomosis, and the development of large hematomata in the pelvis following combined abdomino-perineal resections of the rectum. One hematoma with subsequent abscess following hysterectomy is noteworthy since this complication has not been seen in many years prior to dicumarol therapy.

Prophylactic superficial femoral vein interruption has been done on 871 patients between 1943 and 1947 inclusive. Table IV illustrates the gradual adoption of this procedure from 15 patients in 1943 to 317 in 1947. The prophylactic use of this method now represents 58 per cent of all femoral vein interruptions done in our hospital. This brings out the confidence we have gained in this type of protection. Since we have a definite increase in the age of the patient and severity of lesion in recent years it is evident that now a higher percentage than formerly of those treated on the Surgical Service can be logically protected from thrombosis and embolism by this method. It does, to some extent, involve medical patients also since the ratio of fatal embolism

TABLE IV

INCIDENCE OF THERAPEUTIC AND PROPHYLACTIC FEMORAL VEIN INTERRUPTION IN 2,131 CASES

Massachusetts General Hospital—1937 to January 1948

	Therapeutic	*Prophylactic*		*Total*
1937-1942	202	0	0%	202
1943	150	15	9%	165
1944	208	72	26%	280
1945	214	178	45%	392
1946	259	289	53%	548
1947	227	317	58%	544
Total	1,260	871		2,131

is about the same as the number of beds available for medical and surgical cases.

In 4 of these patients treated by prophylactic femoral vein interruption, fatal embolism occurred. In 3 of these there was no past or present evidence that thrombosis was already established before femoral vein interruption was undertaken. The embolism in one of these may have originated in the proximal segment of the superficial femoral vein left in situ. Definite extension into the profunda femoris was found in one and this we believe led to the large propagating thrombus in the iliacs of sufficient magnitude to cause death. We feel that the dangers of interruption of the common femoral is greater than that of fatal embolism originating in the profunda femoris. Also it seems clear to us that the superficial femoral should be interrupted as close to the profunda femoris as is technically possible.

The other death in this group is definitely questionable from the prophylactic viewpoint. The surgeon felt in retrospect that thrombosis was present in the iliac veins at the time of interruption but was overlooked. This patient had been in the hospital twelve weeks under treatment for arteriosclerotic obliterative disease. The prophylactic interruption was done at the time of low thigh amputation. He died suddenly the day of operation and had, at autopsy, massive emboli of both pul-

TABLE V

EMBOLIC DEATHS SUBSEQUENT TO FEM. VEIN INTERRUPTION

PROPHYLACTIC

Age	*Sex*	*Disease*	*Operation*	*Interval between vein inter. and death*
67	M	Ca Sigmoid with Obstruction	Cecostomy, later Resection	16 days
54	F	Ca Stomach	Total Gastrectomy	34 days
63	F	Ventral Hernia	Repair	15 days
78	M	Arteriosclerotic gangrene	Thigh Amputation—12 wks. after admission	8 hours

monary arteries, that appeared to have originated in the iliac veins. The pathologist's impression was that the thrombi were older than the number of hours elapsed between operation and death. However, since it was done on the prophylactic basis by one of our pioneers in this field we think we are justified in including it in the failures of the method (Table V).

It would not be possible to determine accurately the net salvage in this group of 871 patients. We have, however, made an accurate comparison between these and a similar number of patients unprotected by prophylactic femoral vein interruption. We have considered the sex, age, disease, type of operation, and service in the hospital in this comparative study. As seen in Table VI it appears that 37 of these patients might have died of pulmonary embolism if this preventive method had not been carried out. It must be pointed out, however, that other factors may have played a role and we are fully aware of the lack of scientific data desirable in such a report.

THERAPEUTIC MEASURES

Most workers in this field have stressed the routine general measures for the prevention of thrombosis and embolism mentioned earlier in this report. Also we, as others, interested ourselves in specific methods of treatment in nonfatal cases of embolism and thrombophlebitis.

TABLE VI

COMPARATIVE INCIDENCE OF POSTOPERATIVE THROMBOSIS AND EMBOLISM

Age group 65 years or over—January 1, 1948

	Number of cases in each group	*With Prophylactic Vein Interruption*		*Without Prophylactic Vein Interruption*	
		Phlebitis	*Fatal Embolus*	*Phlebitis*	*Fatal Embolus*
Fractures Hip Region	130	3	0	23	10*
Leg Amputation	92	1	1	6	8
Colon Operations	111	5	1	16	6
Gastric Operations	94	7	1	9	4
Resection of Rectum	52	2	0	11	2
Genito-Urinary Surgery	50	4	0	3	2
Biliary Surgery	74	2	0	8	1
Pelvic Surgery	46	0	0	4	1
Hernioplasty	41	2	1	3	1
S.B. Obstruction	21	3	0	2	1
Neuro Surgery	7	0	0	0	1
Appendectomy	24	1	0	2	0
Heart Disease	23	0	0	4	0
Radical Mastectomy	20	0	0	1	0
Pancreatic Surgery	15	2	0	4	0
Esophagectomy	12	0	0	2	0
Miscellaneous	59	3	0	4	0
Total	871	35	4	102	37

* Because of medico-legal jurisdiction autopsy was not possible in all deaths following hip fractures.

Intravenous heparin was our first specific remedy and this drug, valuable as it is, proved in our early experience to be unsatisfactory. It was cumbersome to use and costly to the patient. Also we found it unreliable since one fatal embolism occurred during its use and another 48 hours after the patient appeared to be well following fourteen days of therapy. With Homans' influence so near us it was natural that we began to have confidence in phlebotomy, thrombectomy and femoral vein inter-

ruption. Gradually this method of treatment took precedent over all others although many cases were treated by anticoagulants, and procaine sympathetic blocks as well.

That anticoagulant therapy is effective in the hands of many workers is obvious from the numerous reports on the subject. The Scandinavian surgeons have made outstanding contributions to this field.[4, 5, 6] Among the American physicians and surgeons using anticoagulants with satisfaction should be mentioned Murray and Best of Toronto,[7] Allen of Rochester, Minnesota,[8] and Evans and Dee of Boston.[9] The latter deserve great credit for paralleling 57 sudden fatal emboli occurring during the time of their study. All of us have been amiss in not reporting these sudden embolic deaths that come with little or no warning. We are in the process of tabulating these cases in our own institution. Until these are carefully studied it will not be possible to determine the exact value of prophylaxis or treatment in this syndrome. From a purely pathologic viewpoint the number of fatal emboli in relation to the number of autopsies appears to be unchanged. It is obvious that many factors must be taken into consideration. Patients rarely die now of shock, peritonitis or pneumonia and the average age of surgical patients has increased. Also, the magnitude of surgical procedures is greater. Many patients who formerly died of other causes now live long enough to develop thrombosis and embolism.

Since our data on phlebotomy, thrombectomy and femoral vein interruption is available we will discuss this method of treatment further. Up to January 1st, 1948, 1,260 patients have been so treated in our clinic. The indications are given in Table VII. This shows that there has been a decreasing tendency to await nonfatal infarct from 41 per cent in 1942 to 14 per cent in 1947. Definite signs of thrombosis on examination of the legs has declined from 59 per cent in 1942 to 24.6 per cent in 1947. Recently a small percentage of patients have been subjected to superficial femoral vein interruption on the basis of the clinical chart only. We have observed that when there is a concomitant rise in temperature, pulse and respiration in an otherwise normal course of events we can be reasonably sure that thrombosis is present and infarct has occurred. In many of our massive embolic cases we could find this warning sign on the clinical chart in retrospect. These figures, as will be observed, are greatly influenced by our attitude regarding prophylactic femoral vein interruption.

TABLE VII

INDICATIONS FOR FEMORAL VEIN INTERRUPTION

Massachusetts General Hospital—1937-1947—2,131 Cases

	1937-42	*1943*	*1944*	*1945*	*1946*	*1947*
Chest pain as first symptom	41.0%	34.5%	32.5%	23.0%	16.4%	14.0%
Leg sign as first symptom	59.0%	56.3%	41.8%	33.7%	30.5%	24.6%
Positive clinical chart sign	0	0	0	0	0.4%	3.1%
Prophylactic Interruption	0	9.2%	25.7%	43.3%	52.7%	58.3%

TABLE VIII

EMBOLIC DEATHS SUBSEQUENT TO FEM. VEIN INTERRUPTION

THERAPEUTIC

Age	*Sex*	*Disease*	*Operation*	*Interval between vein inter. and death*
47	F	Intract. Facial pain	Lobotomy	23 days
74	F	Diabetic gangrene	Thigh amputation	2 days
74	M	Ca Stomach Inoperable	Peritoneoscopy	38 days
66	M	Ca Stomach	Subtotal Gastrectomy	9 days
76	F	Cataracts	Enucleation	8 days
77	M	Phlebitis and Pulmonary Infarct	Medical patient	13 days

In this group of patients there were six who died as a result of further emboli. All of these patients had had nonlethal embolic processes prior to femoral vein interruption. The average age of this group was 69 years. Two had advanced cancer originating in the stomach, one was a diabetic with gangrene, one was hypertensive and had undergone bilateral cataract operations, one had had pre-frontal lobotomy for intractable facial pain and the other had had numerous previous attacks of phlebitis (Table VIII).

One can conjecture that many of the patients who survived would have died of embolism had nothing specific been done to prevent it. The net salvage is again impossible to determine. It must be borne in mind that these patients were saved the prolonged convalescence formerly seen in the treatment of thrombophlebitis. Post-phlebitic edema and ulcer does not occur in patients treated specifically in the early course of thrombophlebitis.

A small percentage of patients treated by phlebotomy, thrombectomy and femoral vein interruption had continued pulmonary infarcts. Occasionally these patients had pain and swelling and tenderness in the extremity where the thrombosis existed previously. These were treated by anticoagulants and lumbar sympathetic procaine blocks after vein interruption. Rarely it was necessary to ligate the inferior vena cava in patients who continued to have infarcts in spite of all these methods of treatment.

Summary and Conclusions

1. Up to January 1, 1948, over 2600 patients at the Massachusetts General Hospital have had specific efforts made to prevent or treat thrombosis and embolism. Some patients received a combination of methods accounting for the variation in total figures.

2. General prophylactic measures only were used in most patients under the age of 30. Specific treatment was indicated in a few of these because of the previous history of phlebitis or the type of lesion present. Therapeutic specific measures were carried out when indications of thrombosis or infarct occurred.

3. Four hundred and ninety-six patients between the ages of 40 and 65 were treated prophylactically by small doses of dicumarol postoperatively. None of these died of pulmonary embolism. The hemorrhagic dangers associated with the use of this drug are stressed. We believe that anticoagulants cannot be safely used empirically and that careful laboratory and clinical control is necessary.

4. Prophylactic bilateral superficial femoral vein interruption was done on 871 patients whose age, debility or disease indicated that a high percentage of them would be likely to develop thrombosis of the leg veins. Of these, four died subsequently of pulmonary embolism. This was a highly vulnerable group of patients and based on comparative experience there might have been expected 37 deaths from

embolism.

5. One thousand two hundred and sixty patients were treated by phlebotomy, thrombectomy and femoral vein interruptions after signs or symptoms indicated that thrombosis had occurred. Of these six died of further emboli. It is estimated that 60 of these might have succumbed if specific therapy had been withheld. In a small percentage of these patients anticoagulants and lumbar sympathetic procaine blocks were also used.

6. Deaths from sudden massive embolism still occur in our hospital. These are often without warning and in patients who have had no specific prophylactic measures instituted.

7. The diminished mortality from shock, infection and pneumonia in recent years results in thrombosis and embolism as a more prominent cause of death than formerly noted. Statistically a higher percentage of patients coming to autopsy now will reveal massive pulmonary embolism as the cause of death than was observed ten years previously.

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THE EARLY RECOGNITION OF POST-OPERATIVE VENOUS THROMBOSIS*

Increased Prothrombin Activity As An Aid To Diagnosis

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THE problem of venous thrombosis in the post-operative patient or in any patient who is confined to bed, has always been a challenge to the clinician and in spite of extensive laboratory and clinical study, it still presents many unanswered problems. The dramatic and often fatal complication of pulmonary embolism has justifiably received the greatest amount of attention, but the problem of the chronically swollen extremity and the post-phlebitic ulcer are equally perplexing. During the past decade, there have been rapid advances both in our understanding of the basic pathology and in methods of therapy, but the true etiology of the condition is unknown and there is no reliable means of predicting which individuals are liable to develop thrombosis and its complications. There is heated discussion between the advocates of proximal vein interruption and those who champion anticoagulant therapy, but if these two methods of therapy are to stand the test of time, there must be individualization of each patient and in many instances, one method should complement the other. There is great need for some laboratory or clinical method by which thrombosis can be predicted in the individual patient.

Our understanding of the manner in which venous thrombosis develops has been modified as a result of extensive investigation of the post-operative patient and of the conditions found at autopsy. The source of pulmonary emboli has been considered in the past to be almost entirely the thrombi formed about the site of an operation or in the small pelvic veins of the prostatic or ovarian plexuses. Small emboli

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undoubtedly do arise from these sources, but they are probably not the origin of large emboli or the massive fatal embolus. It is now believed that the veins of the leg are the more common source of emboli and that the most dangerous type of thrombus is that which develops in the small veins of the plantar aspect of the foot or in the calf and propagates proximally into the large veins of the legs without causing the typical signs of venous thrombosis. Homans[1] in 1934 suggested that bland thrombosis of the calf veins without inflammatory reaction was the source of multiple pulmonary emboli and was one of the first to perform proximal vein ligation. There is general agreement at present that the leg veins are the most common source of emboli. Denecke, and Olow[2] showed that the earliest symptoms are in the calf and plantar regions. Roessle[3] in 1937 and Neumann[4] in 1938 demonstrated in autopsy material that the calf and plantar veins are the common sites of thrombosis.

The modern concept of the pathogenesis of venous thrombosis differs from earlier opinions on the subject. In the past, femoral-iliac thrombophlebitis was considered to be the result of infection and thrombosis in the large veins of the thigh and groin with resultant venous obstruction, edema and the signs of phlegmasia alba dolens. This process probably occurs, but the clinical picture of the swollen, painful leg of thrombophlebitis more commonly develops as a result of thrombosis in the small veins of the calf or foot with propagation of the thrombus proximally until the entire femoral vein is occluded by a thrombus (Frykholm,[5] Bauer[6]). In the earliest phase, a coagulation thrombus occurs in the small veins which may give no physical signs or symptoms. This may propagate proximally in the popliteal and superficial femoral vein without being attached to the wall of the vein so that the thrombus is actually waving in the blood stream and may at any time, break free as an embolus. This is the Bland Thrombosis of Homans[7, 8] or the Phlebothrombosis of Ochsner and DeBakey.[9] If the process continues, the clot then becomes attached to the vein wall, the tributary veins become occluded by thrombi, and the typical signs of phlebitis become evident. This is probably the sequence of events in a vast majority of the patients with thrombo-embolism but it does not explain all situations. In post-partum sepsis the inflammatory process involves the pelvic veins and there may be extension of the thrombosis proximally to the iliac veins with massive embolism or via the ovarian veins with multiple

septic emboli. Pulmonary emboli in cardiac patients may have their origin from mural thrombi or from vegetations on diseased valves.

The etiology of venous thrombosis in an individual is usually difficult to evaluate but there are many factors which may be of importance, especially in the post-operative patient. The most obvious of these are physical factors which are present in varying degrees and which theoretically result in conditions favoring intravascular coagulation. Peripheral venous stasis, most marked in the lower extremities, is often present. Abdominal distension with compression of the abdominal veins causes stasis of venous blood in the legs and thighs. Decreased thoracic excursion as a result of pain from upper abdominal and thoracic incisions results in a decrease in the thoracic negative pressure which is so important in promoting venous return. Position in bed with the hips and knees flexed causes angulation of veins. Pressure on the veins of the legs and lack of muscular activity increase venous stasis. The dehydration which may occur after operations increases the viscosity of the blood and favors coagulation.

Post-operative infection plays a part in thrombosis and was present in 75 per cent of the cases of embolism reported by Morton and associates.[10] The infection was not necessarily localized at the operative site but appeared to be a factor when involving any part of the body.

The age of the patient is an important consideration in venous thrombosis, and the majority of fatal pulmonary emboli occur in patients over 50 years of age. The condition of the heart is very important, as even in incipient cardiac failure there is peripheral venous congestion with stasis. The cardiac status also has an important bearing on the end results of pulmonary embolism. In patients who had no demonstrable cardiac disease, 41 per cent of pulmonary emboli were nonfatal; whereas, 92 per cent were fatal in patients with cardiac disease, and no patient survived a pulmonary embolus if cardiac decompensation was present.[10] Another factor of importance in the older patient is the condition of the vessels. Atherosclerosis is usually considered to be primarily a disease of arteries, but the veins may also be involved.

When the venous circulation is impaired, the irregular intimal surface of an abnormal vein may act as the eddy point at which a thrombus develops. Peripheral vasospasm may contribute to slowing of the circulation and thrombus formation. Varicose veins with their sluggish flow are a particularly susceptible factor.

There are other factors directly related to the altered physiology of the blood during and after an operation. Waugh[11] has shown that there is decreased coagulation time in the post-operative period. He reported a "Heparin-Dilution" method of determining coagulation time which showed a definite decrease in time usually on the third and fourth post-operative days. We have obtained similar results in our laboratory using his method. Crafoord and Jorpes[12] have noted that a larger dose of heparin is rendered inactive in the blood during the first and second post-operative days than at other times and interpret this as indicating hyper-coagulability of the blood. There may also be some alteration in the platelets after operation. Wright[13] believes that there is an increased adhesiveness of the platelets in the post-operative period with an accompanying rise in platelets. Tocantins[14] has found a decrease in the number of platelets on the first, second and third days after an operation with an increase on the sixth and a maximum level on the tenth day. The increase is most marked after sepsis and splenectomy. Laffont and Sirjean[15] found the platelet count elevated several days before puerperal phlebitis developed. Other changes in the blood such as an increase in fibrinogen, hyperglobulinemia, and increased viscosity may contribute to thrombus formation.

Diagnosis of Post-Operative Thrombosis

The diagnosis of frank thrombophlebitis is usually not at all difficult, and the tender, swollen extremity associated with chills and fever is characteristic. The diagnosis of the early bland thrombosis or phlebothrombosis is much more difficult, and requires careful observation of the patient. An unexplained rise in the pulse and/or the temperature may be the first warning sign and demands careful examination of the legs (Allen et al.[16]). Bauer[6] has called attention to the symptom of restlessness and we have been impressed by this as an early symptom. The patients have a sense of "something being wrong," they are restless and worried. Aching or cramp-like pain in the calf may be the first warning. Examination may reveal tenderness in the calf and pain with dorsiflexion of the foot (Homans), the muscles may be tense or spastic and there may be cyanosis of the foot which is evident in dependency and in some early cases, evidence of vasospasm, i.e., coolness and hydrosis. In the early stage, venography has been of assistance in the diagnosis but venograms are difficult to interpret and the diodrast may be irritating

to the veins. There is a tendency at present to rely more on clinical signs and less on venography in the diagnosis of quiet thrombosis. In spite of the most careful observation, there still remains the patient who has a sudden pulmonary embolus without previous warning of thrombosis. There is urgent need for a clinical or laboratory test to detect incipient thrombosis and it is for this purpose that we wish to present our preliminary studies of prothrombin activity in the post-operative patient.

Our first efforts to find a laboratory test which might be of value in detecting early thrombosis was stimulated by the work of Waugh and Ruddick.[11] They used a heparin dilution method of determining blood coagulation time and found the time was decreased during bed rest, in acute inflammatory conditions, in the presence of hemorrhage, and during the post-operative period. Using this method we have found marked reduction in coagulation time in several post-operative patients who developed thrombosis. The test was unsatisfactory for extensive clinical use as it required 12 cc. of blood for each determination and the end point of coagulation was so difficult to read that interpretation of the results was difficult. A decreased prothrombin time was also noted in those patients who developed thrombosis. The determination of prothrombin activity of the plasma is a much simpler laboratory procedure and it seemed worthwhile to study its alterations in the post-operative patient.

There are conflicting reports in the literature concerning the relation of prothrombin activity to thrombosis. Tuft and Rosenfield[17] concluded from their studies using dilute plasma, that an acceleration of prothrombin time is not suggestive evidence of a tendency to thromboembolism. Hurn, Barker and Mann[18] found that the levels of antithrombin and prothrombin are often outside observed normals in patients having a tendency to thrombosis, but that high and low values are present in about equal numbers. Levy and Conroy[19] found decreased prothrombin times during ether anesthesia with a return to normal within 24 hours after the operation. They used the bedside method of determining prothrombin time. The work of Bancroft and Stanley-Brown[20] gives support to the thought that prothrombin activity may give a clue to thrombosis. They determined the "clotting index" according to the formula—C.I. equals $\frac{\text{Prothrombin} + \text{Fibrinogen}}{\text{Antithrombin}}$. An

index of 1.0 or over indicated a tendency to thrombosis and one of 0.3 or less, a tendency to bleed. In a series of post-operative patients, 65 per cent had a normal clotting index and an uneventful convalescence. Thirty-five per cent had a high index and although no frank signs of phlebitis developed, this group all had fever and a prolonged convalescence without any demonstrable cause. Patients with phlebitis all had high indices as did seven patients with pulmonary emboli. They studied patients pre-operatively and on the seventh and ninth post-operative days, and believed that a high index indicated a tendency to thrombosis. Shapiro[21] found a hyperprothrombinemia in patients who had venous thrombosis or a pulmonary embolus. He determined prothrombin time on diluted (12.5 per cent) plasma as well as on whole plasma and found the most consistent decrease in the dilute plasma determination. His results using whole plasma were variable and at times he found a decreased prothrombin activity when thrombosis was actually present. He concluded that a decreased prothrombin time found with dilute plasma was an aid in the differential diagnosis of thrombosis.

Method

Our method of study has been as follows:—Prothrombin activity is determined pre-operatively (the morning of operation) and in the evening after operation. Daily determinations are made each day through the sixth post-operative day. This procedure was followed in a series of 68 surgical patients and 122 obstetrical patients. The initial results indicated that values on the third post-operative day were most significant, and a large series is now being studied doing determinations on the first and third post-operative days. The method used for determining prothrombin activity is as follows and is essentially that described by Quick.[22]

1. *Preparation of thromboplastin:* A fresh human brain is stripped of vessels, gross blood washed off with normal saline, and the tissue macerated by beating at medium speed in an electric mixer. Water and lipids are extracted with large volumes of acetone at low temperature; usually four changes of acetone are required. The granular mass is then placed in a vacuum desiccator and the acetone removed by oil suction pump. The dry powder is kept in a desiccator under refrigeration. For use, 0.3 gm. of the dried powder is suspended in 10 cc. normal saline and the mixture digested at 50-55° C. for 20 minutes with frequent

shaking. It is then centrifuged at 1500 RPM for 5 minutes and the turbid supernatant fluid pipetted off. This is mixed with equal parts of .024 M calcium chloride solution and the mixture placed in a water bath at 37° C. just prior to use.

2. *Standardization of thromboplastin:* Determinations are run in quadruplicate on two fresh plasma samples from each of five normal individuals. Dilutions of 5, 10, 15, 20, 25, 40, 60 per cent, and whole plasma are used and a curve constructed from the average values. Prothrombin activity of an unknown is calculated from this curve.

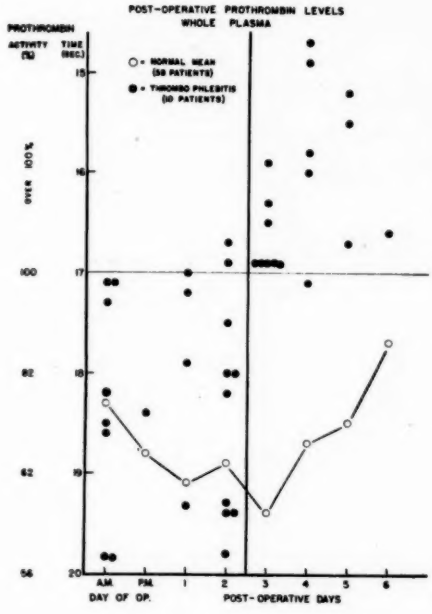
Different individuals may obtain dissimilar results because of differences in reaction time, so they must run checks against each other or carry out separate thromboplastin standardizations. All determinations in this series were done by one individual (R. S.).

3. *Sampling:* Blood is drawn in a dry syringe, avoiding hemostasis as much as possible, and transferred to bottles containing dry oxalate mixture (.006 gm. ammonium oxalate and .004 gm. potassium oxalate in 5 cc. blood). All blood samples in this series were taken by one individual (R. S.) to avoid possibility of error. Hemolyzed or partially clotted blood is not used.

4. *Determination of prothrombin activity:* Blood is centrifuged at 2000 RPM for 10 minutes and the plasma pipetted off. Determinations are run on whole plasma and on plasma diluted to 25 per cent (1:3) with normal saline; 0.1 cc. plasma is pipetted onto a clean watch glass which is placed in the water bath at 37° C. To this is added 0.2 cc. of the thromboplastin-calcium chloride mixture; at this moment the stop watch is started. The mixture is stirred constantly with a glass stirring rod; the end point is reached when clot formation is first observed. A black background facilitates observation of the end point. Determinations are run in triplicate.

Observations

The prothrombin activity of the plasma has been determined in 68 post-operative patients. In 10 of these patients thrombosis developed, and the remaining 58 had no complications. Most of the patients selected were over 50 years of age undergoing major abdominal or chest surgery, or having a history of previous thrombophlebitis. Graph I shows the mean of prothrombin activity in the 58 post-operative patients who did not develop thrombosis. Following operation the pro-



GRAPH I

Hyperprothrombinemia in 10 patients who subsequently developed venous thrombosis. Black dots represent single prothrombin determinations.

thrombin activity decreases (prothrombin time increases) during the first three days and the lowest level usually occurs on the third day. After the third day the level increases and returns to normal about the sixth day. Young individuals have a more rapid return to the pre-operative level—usually by the third or fourth day—and the curves are more variable. Only the average levels of prothrombin activity of whole plasma are plotted on the graph but Table I records the average prothrombin times of both whole and dilute plasma and their statistical variations. There is less variation in the results obtained with whole plasma than with dilute plasma.

The prothrombin activity of whole plasma in patients who developed thrombosis is also shown in Graph I. The ten patients did not

TABLE I

POST-OPERATIVE PROTHROMBIN LEVELS
58 NORMAL PATIENTS

	No. of Patients		*Mean*		*Standard Deviation*		*Coeff. of Variation*	
Dilution	100%	25%	100%	25%	100%	25%	100%	25%
Pre-op (A.M.)	56	50	18.3	33.2	1.25	2.82	.07	.08
Post-op (P.M.)	20	13	19.0	36.7	1.78	2.31	.09	.06
Post-op I	27	21	19.1	35.4	1.27	3.94	.07	0.11
Post-op II	32	26	18.9	33.7	1.31	2.58	.07	.08
Post-op III	17	12	19.4	33.3	1.31	2.20	.07	.07
Post-op IV	24	19	18.7	32.0	1.27	2.43	.07	.08
Post-op V	15	12	18.5	33.9	1.79	3.46	0.10	0.10
Post-op VI	8	7	17.7	31.5	1.71	2.27	0.10	.08

Whole Plasma 17.0 sec. equals 100% activity
Dilute Plasma 29.2 sec. equals 100% activity

all have determinations every day but it is evident that their prothrombin activity varied much more than the normal values on the first and second days and were in general above normal. All of the patients who developed thrombosis were above 100 per cent on the second and third days—two patients on the second and eight on the third day. The increase in prothrombin activity was usually abrupt and was significantly higher in every instance than the values obtained in normal patients. In this group of ten patients, five were treated with anticoagulants and five were not. In some untreated patients, the prothrombin values remained high after the third day but in many the values return to a normal level even though thrombosis is present. A larger series of patients is being gradually accumulated and the results are similar to this group. It appears that a sudden rise of prothrombin activity on the second or more often, the third day is a significant warning of thrombosis. This increased activity has been helpful in non-surgical patients in whom the diagnosis of early thrombosis has been questionable, but once thrombosis is established, the activity has usually returned to normal levels.

Discussion

It is too early to draw far-reaching conclusions from the data which have been presented but the consistent results obtained permit tentative impressions. The hyper-prothrombinemia which has appeared rather uniformly on the third post-operative day in patients who subsequently developed clinical evidence of thrombosis suggests that at this time the thrombotic process is just beginning in small veins. The increased prothrombin activity appears to be a transitory phenomenon as the prothrombin time in untreated patients is often normal during the clinically recognizable phase of the disease. It is possible that the increased prothrombin activity occurs just before actual clotting begins and is a warning that the stage is being set and changes are occurring in the blood which result in thrombosis. Whether or not thrombosis has actually begun when the change in prothrombin activity occurs, this seems the ideal time for the use of anticoagulant drugs.

This warning of impending thrombosis is non-specific in that it seems to be present whenever a thrombus is forming any place in the vascular system. In several patients, the activity has been over 100 per cent and on the following day, a small thrombus has been palpable in an ankle vein which had been used for intravenous infusion during the operation. A positive test appears to be a warning that the patient should be observed carefully and perhaps that prophylactic anticoagulants should be given. It is impossible as yet to judge the diagnostic importance of the test. In the series of patients studied, no one has developed clinical evidence of thrombosis who did not have a positive test. Two patients have had a sudden rise of prothrombin activity on their third post-operative day without developing clinical evidence of thrombosis. Both patients were under 30 years, one had an appendectomy, the other a herniorrhaphy, and both were out of bed and walking on their first post-operative day. It is possible that the test is less significant in young people as the greatest variations in prothrombin activity occur in this age group. Older individuals have more uniform prothrombin activity curves following operation and the change suggesting thrombosis is more pronounced.

It is of interest that the increased prothrombin activity is more uniformly evident in the whole plasma determination than in the dilute plasma which is a more accurate test. If the condition is only hyper-

prothrombinemia, it should be equally evident in both methods. It is possible that some factor other than prothrombin is involved. This is only conjecture and the exact situation has not been investigated.

Prevention of Thrombo-Embolic Complications

The greatest efforts to prevent thrombosis should be directed toward patients in the older age groups as 80 per cent of the complications occur in patients past forty years of age and 50 per cent occur between fifty and seventy-five years (Ochsner,[23] Stich,[24] Allen[25]). Every effort should be made to prevent venous stasis by encouraging active exercise of the patient while in bed and by early ambulation. Fowler's position on the Gatch frame should not be used as it causes constriction and angulation of the great veins. Abdominal distension should be prevented, and deep breathing should be encouraged. The cardiac status of older patients should be improved as much as possible. The operation should be done with minimal trauma, and anoxemia should be avoided. Of greatest importance is the prevention of shock and dehydration which result in sludge formation and increased viscosity of the blood. The prevention of infection is very important. Peripheral vasospasm is a cause of peripheral venous stasis and cold extremities should be treated with heat or other measures to overcome the spasm.

A great amount of discussion now centers about the use of prophylactic vein interruption or anticoagulants to prevent thrombo-embolism. Advocates of either method have published convincing statistics supporting their particular method and at the present time, it is impossible to form an unbiased opinion as to their relative merits. Allen and his co-workers[16, 25] are the foremost advocates of vein ligation, the Swedish workers (Crafoord, Jorpes and Bauer) have had the most experience with heparin, and Barker[26, 27] exemplifies the advocates of dicumarol. A comparison of published statistics is given in Table II. These results are all from a series of older patients in whom thrombo-embolism is most common and in operations in which the danger is greatest. Whichever method one prefers, no one can deny that great progress is being made.

In spite of these advances in prophylactic treatment, there still remain many problems. Crafoord and Jorpes' experience with prophylactic heparin seems ideal, but heparin is expensive, it must be given parenterally, and the control of dosage is a major problem if all operated

TABLE II

PROPHYLACTIC TREATMENT OF THROMBO-EMBOLISM

Comparison of Vein Ligation and Anticoagulants

Treatment	*Number Patients*	*Thrombosis and Embolism*	*Fatal Embolism*	*Authors*
None	302	11%	2.9%	Craaford &
Heparin	325	0	0	Jorpes
None	832†	3.9%	.07% (6 cases)	Edgar Allen
Dicumarol	832	0.4% (3 cases)	0	et. al.
None	458*	12%	5.7%	Arthur Allen
Vein Ligation	458	1.1% (5 cases)	1 case	

† Estimated Complications—Abdominal Hysterectomy.
* Selected cases—Older Age Group.

patients over forty are to receive it. Dicumarol is not expensive, but its dosage is more difficult to control than heparin and requires a trained technical staff. Vein ligation involves a bilateral surgical procedure and we do not know as yet, the late complications of interruption of the superficial femoral vein. We are very hopeful that continued experience will substantiate our present feeling that a sudden increase in prothrombin activity to above normal on the second or third post-operative day indicates incipient thrombosis. At present, the patients having a positive test are given dicumarol in adequate doses. It would probably be more logical to give heparin until the dicumarol effect is evident. For the advocates of vein ligation, this test should help in selecting the cases for treatment.

There has been considerable interest in the prevention of post-operative thrombosis and many reports have shown an impressive decrease in thrombosis and pulmonary embolism. The success of prophylactic endeavors has been properly attributed to the use of vein ligation or anticoagulants but the importance of careful post-operative care must not be neglected. Whenever a clinician becomes interested in this problem the patients are followed more carefully and more attention is paid to general preventive measures such as hydration, leg exercises, etc., which are important factors in minimizing this complication. Also

the difference between control and treated series will be more striking because of alertness in diagnosing thrombosis. There can be no doubt but that many patients have minor thromboses which are completely missed unless attention is being focused on the problem.

At present no final decision can be made as to the relative merits of vein ligation and anticoagulants in the prophylactic treatment. Results in one series of patients treated by both methods are very similar (Table II). The results obtained with heparin and dicumarol are a little better than with vein interruption and the low incidence of thrombosis and embolism in each group is very impressive. There are certain contraindications to anticoagulant therapy which should be carefully observed. It is contraindicated in hemorrhagic diseases and probably should not be used after operations which have a tendency to post-operative bleeding from a large denuded area such as after prostatectomy, Miles operation, and in some chest cases. Dicumarol should not be used in patients with liver disease. Most important of all, neither heparin nor dicumarol should be used unless laboratory facilities are available to carefully follow the course of therapy. Both of these drugs are satisfactory anticoagulants and are usually started simultaneously—the heparin for its immediate effect until the dicumarol effect is evident.

A great advantage of anticoagulants is their general effect on coagulation and they should be effectual wherever thrombosis exists, whereas vein ligation prevents embolism only from the tributaries of the vein distal to the ligature. Also they prevent propagation of a thrombus into tributary and collateral veins. Prophylactic vein ligation is usually performed bilaterally just distal to the profunda femoris vein and is effectual in preventing embolism because of the high percentage of emboli which have their origin from the veins of the leg. It is a relatively simple procedure which can be performed under local anesthesia with little risk. It does not require laboratory control and most patients can be immediately mobilized. The danger of hemorrhage is not a factor. Against vein ligation are possible late effects of ligating the superficial vein such as edema, development of varices, and ulceration. Only by prolonged observation can this feature be evaluated. Also it is difficult for most surgeons to sacrifice a major vein if definite disease does not exist.

It should be emphasized that our experience with the prothrombin activity as a test of incipient thrombosis is limited and no far-reaching

conclusions are being drawn at present. It is difficult to obtain a large series of test cases and this preliminary report is being made so that others may test its efficacy. The abrupt increase in prothrombin activity has occurred on the third post-operative day and seems to be a warning of thrombosis. It is a transitory situation as prothrombin activity is often normal when thrombosis is clinically present. The change is more consistent when whole plasma rather than dilute plasma is used in the determination of prothrombin time. The dilute plasma determination is a more accurate index of liver function and is used to follow patients being treated with dicumarol. Prothrombin activity is not an index of the extent of thrombosis. The test has not been evaluated in patients confined to bed for long periods because of medical conditions or fractures.

Conclusion

1. Using Quick's one stage method of determining prothrombin activity, we have been able to detect a significant change in the whole plasma of patients who subsequently showed signs of venous thrombosis.

2. This is suggested as a test for the early diagnosis of post-operative thrombosis and as a basis for selecting patients who should receive prophylactic anticoagulant therapy.

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THE EARLY DIAGNOSIS OF CANCER*

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Most forms of cancer begin in a single cell or in a small group of cells localized in a single organ or tissue. At this early stage the disease is, of course, perfectly curable surgically if we could but detect its presence. Sooner or later, however, a stage is reached when the disease is so far advanced locally that it cannot be excised, or it escapes as a metastasis through the blood or lymph stream to distant points and the chance of cure is gone. Early diagnosis is in this sense more important in cancer than in most diseases, for it often means the difference between success or failure, life or death.

We may think of the diagnosis of a carcinoma as a drama in three acts. In the first act the patient perceives the signs or symptoms of her disease, and after a varying period of delay, goes to consult her physician. Her perception of her signs or symptoms depends first of all upon her keenness of observation and her sensitivity. An alert, intelligent woman is apt to detect a tumor of her breast long before a dull, stolid individual. Education, too, plays a part. A woman who has learned the significance of a breast tumor and who has been taught to examine her own breasts has a great advantage over one who lacks such education. Here is the greatest opportunity for useful propaganda that the cancer societies have. At some time in the early adult life of every individual she should be taught the chief signs and symptoms of the most common forms of cancer, and the importance of going at once to consult a physician when any one of them is discovered. The cancer societies have not as yet worked out any very good way of accomplishing this.

Unfortunately their propaganda has often taken another direction, one which in my opinion, often actually hinders early diagnosis. It is the propaganda of fear. If you read over the leaflets and magazine

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articles sponsored by the cancer societies, you will find that nine out of ten frighten the reader. I have before me as I write a leaflet distributed by the American Cancer Society which illustrates this point very well. In bold red letters we read "No one is safe from cancer. Every three minutes someone in the United States dies of cancer. No one is safe. There is one chance in eight that you yourself will be a victim of this deadly killer. . . . Cancer is the greatest and cruelest killer of American women between the ages of 35 and 55. . . . Guard those you love. Give to conquer cancer."

Now this may be the propaganda line that is most effective in raising money. But it is not the kind of propaganda that is most apt to help the woman who has discovered that she has signs or symptoms suggestive of cancer. She is already frightened enough without being further terrified by what she reads. She may well be too frightened to face the fact that she may have cancer—too frightened to go to her doctor. In my own studies of the manner in which cancer is diagnosed I have come to believe that fear plays a considerable part in the delay that many patients allow before consulting a physician. Certainly it is the next important factor after ignorance in causing delay.

What our patient in the first act of our drama needs is not more *fear* but more *courage*. She needs to be told, and made to believe, that she can be cured. This is the kind of propaganda that will do the most to persuade her to go at once to her doctor. Let us not lose sight of this fundamental fact. What we are trying to do is to get the patient to go to her doctor at the earliest possible moment.

I should like to see the propaganda of the cancer societies written not by publicity agents, familiar with the technique of raising large sums of money, but by wise physicians, aware of the forces that move sick human beings.

The second act of our drama takes place in the physician's office. The patient has done her part—she has conquered her fear and gone to her doctor. It is now his turn to do his part. He takes his history and examines the patient. If he is to detect cancer, he must *suspect* its presence, for unless he suspects that he is dealing with malignant disease, he will not carry out the diagnostic tests necessary to prove the nature of the lesion. The development of this suspicious state of mind depends upon his alertness and his clinical knowledge of cancer. There is clear evidence to indicate that medical education, as it exists

at present, fails to provide physicians with sufficient clinical training in cancer diagnosis. In a recent study of the manner of diagnosis of breast cancer in patients coming to our clinic, we have shown that about one out of every four patients receives incorrect advice from the first physician she consults regarding her breast cancer. Data from other clinics have yielded similar results. In the face of this factual evidence, medical school authorities have in general continued to deny that there is any need of change in the curriculum. Those who do not realize the need for a thorough revision of the medical school curriculum are living in an ivory tower, unconscious of the realities of the practice of medicine.

While we are trying to change the medical curriculum to improve our training of under-graduates in cancer diagnosis, we feel strongly the necessity of attempting to instruct practicing physicians how better to diagnose cancer, and this afternoon's lecture is a small step in this direction.

The third act of our drama records the steps by which the physician proves the presence of cancer. The action occurs in most instances in a hospital, where the roentgen ray laboratories, operating rooms, and pathology laboratories that are needed for the various diagnostic tests, are available.

It is unfortunately as yet impossible to draw a little blood from a patient in your office and send it off to a laboratory for some sort of analysis that will reveal the presence of cancer. There is no chemical or physical reaction of body fluids or tissues that is diagnostic of cancer. There is a continual succession of such claims, but when tested critically, they have all proved to be false. Some of our newspaper writers add to the confusion by interpreting any statement about cancer as news, and printing it. This is all very well for general topics, but medicine in general and cancer in particular is not a proper subject for hasty publicity. The truth, if it *is* the truth, can do no harm, but it often takes a long time to establish.

In our own institution we have recently had an example of an entirely unjustified claim of a diagnostic test for cancer. It was claimed that the blood serum in cases of cancer has a fluorescent quality not present in normal serum. Before the claim had been adequately checked, an announcement had been made at a medical meeting which was picked up and given publicity in the newspapers. Careful revalua-

tion of the test in our own clinic has proved that it is of no diagnostic value. Because of the publicity given the test, a good deal of time and money have been wasted on it.

In proving the presence of cancer the physician has only roentgen ray studies and the microscopical interpretation of cells and tissues to rely upon. These are highly technical disciplines requiring skilled specialists. Many smaller hospitals can not provide adequately trained roentgenologists and pathologists, and their lack is one of the greatest handicaps that physicians face today in dealing with cancer. The lack of pathologists skilled in interpreting Papanicolaou smears has but recently been felt in many clinics, even some of the largest. The general lack of pathologists properly trained in the interpretation of frozen sections is less well known but certainly more important. There are methods for preparing excellent paraffin sections within twenty-four hours, a service of great help in expediting the diagnosis and treatment of cancer. Ideally all of these services should be available in every hospital. There is today not only a lack of money to pay pathologists, but a great shortage of adequately trained men. In our laboratory of Surgical Pathology at the College of Physicians and Surgeons, Dr. Stout is doing his part to remedy the situation by conducting a course for graduate training in surgical pathology. An average of twenty-five men are enrolled in it.

We will review the diagnostic problem for each of the most common types of cancer. These are, in increasing order of frequency: Cancer of the lip, the oral cavity and pharynx, the urinary bladder, the ovary, the lung, the rectum and recto-sigmoid, the colon, prostate, stomach, skin, uterus, and breast. The data which I will use as to the incidence of the different forms of cancer are based upon the recent New York State morbidity data.

Epithelioma of the lip: Epithelioma of the lip is about fourteen times as common in men as it is in women. It is, of course, overwhelmingly a disease of the lower lip, the upper surface of which is exposed to the sun. Women today are almost as heavy smokers as men, yet they have far less lip cancer. This fact, I believe, is a strong suggestion that the chief cause of epithelioma of the lip is sunlight. We should therefore look particularly for the disease in out-of-door men, such as policemen, sailors, and farmers. Any change in the epithelium should raise a suspicion of beginning epithelioma. In the

earliest stage of the process the keratin layer piles up to form a scale, or crust, which repeatedly falls and reforms. Eventually, when epithelioma develops from the basal layers of the epidermis and begins to grow down into the corium and finally into the musculature of the lip, induration and ulceration occur. A small wedge biopsy should always be done when any induration or ulceration is discovered in the lip. This is a simple office procedure, best done with a sharp knife after a small amount of novocaine has been injected into the lip.

At an earlier stage, when the lesion consists only of piling up of keratin to form a scale, the best procedure is the excision of the involved segment of the lip surface. At this early stage, biopsy will not show fully developed epithelioma, yet the area of diseased epithelium is a constant threat and had best be removed.

Epithelioma of the oral cavity and pharynx: Epithelioma of the oral cavity and pharynx is three or four times as common in men as in women. It is our clinical impression that it usually develops in patients whose oral hygiene is bad. Decayed teeth and the excessive use of tobacco both contribute to the abuse of the oral mucosa. Such patients usually ignore slight abnormalities in the mouth and only come for diagnosis when the lesion is well advanced and becomes painful. This, then, is a type of cancer in which early diagnosis is theoretically easy but is rarely achieved in practice. Our propaganda for the public should aim at educating the individual as to the importance of good oral hygiene and of consulting a physician at once when any abnormality in the oral mucosa is discovered.

The physician on his part should be suspicious of every erosion, induration, or tumor in the mouth, and should biopsy it forthwith. This is a simple procedure, easily done in the office, with anesthesia obtained by the surface application of 2 per cent cocaine. A wedge of tissue three or four millimeters in diameter, excised with a scalpel, is sufficient.

Dentists often see these mouth lesions first, particularly when they develop around teeth. They are accustomed to see granulomas developing around teeth and in the gums following tooth extraction, and they tend to regard all such lesions as benign. This is not a safe practice, for epithelioma sometimes develops in this guise. All such lesions should be biopsied before they can safely be regarded as granulomas.

Leukoplakia developing in the mouth requires special mention. It is, of course, merely a thickening of the keratin layer of the epithelium, but it often precedes epithelioma. The thin, pale, filmy type of leukoplakia need not cause alarm, but the thicker patches of leukoplakia, which are often seen accompanying the thinner variety, must be regarded as precancerous. They should be excised or destroyed by cauterization. New areas of this dangerous type of leukoplakia will usually continue to develop, and the surveillance of these patients becomes a life time task. In searching for leukoplakia the mouth should be inspected by daylight, not by artificial light.

Epithelioma of the urinary bladder: Epithelioma of the urinary bladder is the next most frequent type of cancer. It is twice as common in men as it is in women. Unless the lesion happens to develop in the trigone area of the bladder, it may be silent until well advanced. Any hematuria, or unexplained pyuria, is an indication for thorough urological study, including cystoscopy. Lesions developing in the trigone may produce disturbances of micturition, and when these occur in the absence of infection, cystoscopy should always be done. Papanicolaou smears made from urinary sediment have given presumptive diagnosis in some instances but the method is not yet thoroughly tested. It cannot replace cystoscopic study of the bladder.

Carcinoma of the ovary: Carcinoma of the ovary is the most frequent type of malignant disease of the female genital organs, excepting, of course, cancer of the cervix. It is a silent disease in its early stages, and is usually not diagnosed until it has produced peritoneal implants or distant metastases. The finding on pelvic examination of an adnexal tumor when there is no history of pelvic inflammatory disease, is an indication for exploratory laparotomy. In this way ovarian tumors may sometimes be diagnosed at an earlier and more hopeful stage. We must admit, however, that the outlook today for early diagnosis of ovarian tumors is very poor.

Carcinoma of the lung: Carcinoma of the lung during the past generation has shown a more marked increase than any other type of cancer. The disease is about four and one-half times as frequent in males as it is in females. In most instances it develops in the bronchi, and depending upon its situation in the bronchial tree, it produces a varying degree of narrowing and obstruction which causes obstructive emphysema, atelectasis, or various types of infection of the portion of

the lung peripheral to the site of the tumor. Cough, chest pain, dyspnea, and expectoration of sputum, which is sometimes blood-streaked, are the most frequent symptoms. Loss of weight and strength and pleural effusion are late symptoms, which do not interest us here. In many of the cases of lung carcinoma, the secondary inflammatory phenomena mask the clinical picture and lead to the mistaken diagnosis of bronchitis, tuberculosis, abscess, or empyema. Graham has emphasized the importance of atelectasis of a lobe of the lung. If it occurs in a man at or beyond middle age who complains of a cough or pain in the chest, the probability of carcinoma is great.

When carcinoma develops in the small bronchi near the periphery of the lung, most of the symptoms that we have mentioned may be absent. The disease is then silent until symptoms develop due to actual invasion of chest wall or to distant metastases.

Any patient who develops cough, expectoration, or pain in the chest which do not subside within a relatively short time should be studied with the possibility of carcinoma in mind. Our first and most important diagnostic aid is, of course, a roentgen-ray examination. If chest films were made routinely of every patient admitted to the outpatient department or wards of a hospital, a number of relatively early cases of lung carcinoma would certainly be picked up. When the lesion is in a bronchus near the root of the lung and has not yet caused atelectasis, it may be entirely hidden by mediastinal structures, but it soon infiltrates radially from the lung root and produces streaks or nodular shadows, extending in a fan-like manner out from the lung root.

In most cases where a suspicion of carcinoma arises, it is desirable to study the bronchial tree after the injection of iodized oil. This is a harmless procedure and often reveals important additional information. The oil should be injected through a transglottic canula or catheter, with the position of the patient so controlled that the oil enters the lobes that are to be visualized.

Bronchoscopy is, of course, the next step. In perhaps 75 per cent of the cases of lung carcinoma, the bronchoscopist is able to see the carcinoma and prove its nature by biopsy.

Recently the Papanicolaou smear method has been used successfully to diagnose lung cancer in a number of clinics. Its success in diagnosis is said to approach, or even exceed, that of bronchoscopy. The method promises to be a very useful adjunct in the diagnosis of

cancer of the lung.

But even with all these diagnostic aids, the number of patients in whom lung cancer is detected at an early stage is exceedingly small. The rich vascular and lymphatic supply of the lung results in early involvement of the lymph nodes of the lung root. When this occurs, it is already, of course, too late. The surgical results are very depressing, except in the small group of lesions which happen to arise in the periphery of the lung and by good fortune are detected early, before the adjacent chest wall is involved.

Carcinoma of the rectum and recto-sigmoid: The late Daniel F. Jones, a great authority on cancer of the rectum, once said that "there is no disease which can be diagnosed more accurately than cancer of the rectum after the patient once presents himself, and yet there are few diseases which are diagnosed so late in their course." The average duration of the symptoms in Dr. Jones'[1] series was eight months. The early symptoms are any change in the bowel habit or sensation, and bleeding. There may be a slight irritation in the rectum, caused by the presence of the growth, which may give the sensation of not thoroughly emptying the bowel, or enough irritation to increase the number of movements slightly. A slight increase in constipation may be a moderately early symptom, but it is more often a late symptom. When partial obstruction of the rectum develops, there is a constant desire to empty the bowel, and frequent small movements, sometimes mixed with blood and mucus, occur.

Bleeding from the rectum in an adult should always suggest carcinoma of the rectum or colon, no matter what the age of the patient. Whenever bleeding occurs, cancer must be positively excluded by digital and proctoscopic examination.

Digital examination should be done with the patient in proper position. The knee-chest position is not the correct position because any tumor which may be present is pulled out of the pelvis and away from the examining finger in this position. Either the Simms or the lithotomy position is much to be preferred. At least four out of five rectal carcinomas are within reach of the examining finger and can be detected by careful digital examination.

If nothing is found by digital examination, the next procedure required is examination with a sigmoidoscope. This will reveal a carcinoma anywhere below the middle third of the sigmoid, with the

exception that some carcinomas of the recto-sigmoid junction are impossible to see because of the fixation of the lesion to the sacrum and the constriction of the bowel. The fixation of the bowel and the presence of the solid mass can, however, be detected with the sigmoidoscope, and are sufficient evidence for exploratory laparotomy.

Biopsy should always be done when a lesion is discovered.

All patients with symptoms consistent with carcinoma of the rectum or sigmoid should also be studied with a barium enema. By this means a positive diagnosis can often be made, although it must be kept in mind that carcinomas at the recto-sigmoid junction, even when they are well advanced, are sometimes impossible to detect by X-ray study, and a growth in this situation is more likely to be missed than one in any other portion of the large intestine.

Polyps in the rectum and recto-sigmoid provide a special problem. They should always be biopsied if they show suspicious changes, and even if they appear innocuous, they should be excised, for they must be regarded as a precancerous lesion.

The problem of differentiating between carcinoma and diverticulitis of the sigmoid frequently arises. The evidence obtained from barium enema is often the deciding factor. Sometimes carcinoma cannot be ruled out and exploratory laparotomy has to be done. Even then, the surgeon may have great difficulty in deciding what he is dealing with. The inflammatory phenomena secondary to perforation of the bowel are very confusing.

Our hope for earlier diagnosis in carcinoma of the rectum and recto-sigmoid depends primarily upon education of the public to consult physicians when abnormal bowel habits develop, and upon educating physicians so that they will never omit digital, sigmoidoscopic, and roentgen-ray examination in these patients. Unfortunately, it is a fact that we continue to see many patients with cancer of the rectum who have consulted one or more physicians without ever having had a rectal examination. Hemorrhoids are sometimes removed without the true cause of the bleeding being discovered.

Carcinoma of the colon: Carcinoma of the colon is somewhat more common in women than it is in men.

These lesions, from the viewpoint of their symptomatology, fall into two broad groups. Those situated in the cecum and the right half of the colon do not commonly obstruct, for in this part of the

bowel the lumen is large and its contents still liquid. The symptoms which these tumors produce are therefore chiefly due to ulceration, bleeding and infection. Anemia is the commonest symptom and it may be of very marked degree. It is probably caused by the large size of the bleeding surface which these tumors present, for nowhere else in the body are carcinomas with such a large ulcerated surface to be found.

Unexplained anemia, with or without gastrointestinal symptoms, or a right-sided abdominal mass, is an indication for X-ray study of the bowel by barium enema. The so-called double contrast method of examining the colon is an important part of the X-ray study because only in this way can polyps be demonstrated or ruled out with certainty. It is important that a barium enema be given before barium is given by mouth in all cases in which carcinoma of the colon is suspected, because barium given by mouth may plug a stenosing carcinoma and cause complete obstruction.

In carcinomas of the left half of the colon, the obstructive symptoms predominate. Here the lumen of the bowel is smaller and its contents are semi-solid, and the carcinomas which develop in it are often annular and constricting. Our best hope for early diagnosis of these left-sided carcinomas of the colon is barium enema study whenever there is any change in the bowel habit. Even when the symptoms have been present a long time, and obstruction is relatively well developed, the carcinoma may be localized to the bowel and surgical cure easy.

Carcinoma of the prostate: Carcinoma of the prostate is the third most frequent type of cancer in males. From the viewpoint of early diagnosis, however, it presents the greatest problem of all. The earliest symptoms are frequency and difficulty in urination, but these do not usually develop until the disease has infiltrated tissues beyond the prostatic capsule and is well advanced. In the great majority of patients with prostatic carcinoma the disease is so far advanced when the patient is first examined that there is no question about the diagnosis. Cure is rarely, if ever, obtained in these cases by even the most radical surgery. Yet our only hope for earlier diagnosis is the detection by digital examination of small areas of induration in the prostate. We must face the fact that there is at present no practical way of accomplishing this.

Carcinoma of the stomach: Carcinoma of the stomach is the most frequent type of cancer occurring in the male sex, and it is also comparatively frequent in females. The disease is a particularly insidious one, and provides a problem in early diagnosis for which we have found no solution. In the early stages of the disease symptoms are usually ill-defined. Some patients have no symptoms at all; others may have slight epigastric distress or some loss of appetite, or a feeling of loss of strength and inability to get through the day's work.

There is in addition, a group of patients who develop gastric cancer after a long history of attacks of indigestion characteristic of chronic ulcer. In this group, the diagnosis of carcinoma is equally difficult, because it is natural to attribute the new symptoms to the old ulcer. In a patient with an ulcer history, any change in the character of the symptoms should at once raise a suspicion of the onset of carcinoma.

Alvarez analyzed the histories of forty-one physicians with carcinoma of the stomach and showed that even they, who were presumably aware of the possibility of cancer of the stomach, did not obtain a correct diagnosis any sooner than the average layman. If physicians fail to diagnose the disease soon enough in themselves, it is difficult to see how we can hope for improved diagnosis in their patients.

Once a physician suspects that his patient may have carcinoma of the stomach, it becomes his duty to exclude the presence of the disease. Analysis of the gastric contents is probably the least important of the several diagnostic procedures which should be carried through. It has been shown that in many cases of carcinoma, acid is still present, although the majority of patients with the disease have achlorhydria.

Roentgen-ray examination is by far the most important method of diagnosis, but even with this method, the diagnosis of a small carcinoma, particularly of the spreading and infiltrating type, may be extremely difficult for the roentgenologist, particularly when the growth is located in the fundus. He has to rely in his differential diagnosis to a considerable extent upon changes in the mucosal folds of the stomach. Carcinoma infiltrates and obliterates these folds. Unfortunately, the inflammatory process associated with peptic ulcers of the stomach sometimes also obliterates the mucosal folds. In lesions of the antral region, the roentgenologist's greatest difficulty is in differentiating carcinoma from antral gastritis. It is particularly in this group

of cases that gastroscopy is likely to give valuable information which assists in the differential diagnosis.

It is also difficult to distinguish ulcerating carcinoma from peptic ulcer in certain cases. Carcinomas sometimes develop in the margins of peptic ulcers and confuse the roentgenologist.

The flexible gastroscope, although it has been in use only a few years, has proved to be of considerable value in differential diagnosis of lesions of the stomach. The great handicap of the method is the discomfort of gastroscopy which, even when skillfully done, is a relatively trying procedure.

With all these diagnostic aids at his command, the clinician is still unable to diagnose carcinoma of the stomach correctly in a considerable percentage of the earlier cases. Diagnostic difficulties are greatest in the group of patients who have had gastric symptoms for a long time. This fact is illustrated by the frequency with which the resected stomach shows carcinoma, even though the preoperative diagnosis after careful clinical study was benign ulcer. In a number of well studied series of cases of this kind, carcinoma was found in about 20 per cent. Even at the operating table, with the abdomen open and the stomach wall between his fingers, the surgeon is often unable to decide whether or not carcinoma is present.

In years gone by, surgeons hesitated to explore and resect the stomach in these cases because of the high operative mortality, but today the operative mortality for resection in favorable cases is under 5 per cent, and most surgeons are agreed that the wise thing to do if there is any question about the diagnosis is to resect. It is also generally agreed that all supposed ulcers of the greater curvature should be resected, for the great majority of these lesions are carcinoma. Marshall and Welch[2] have recently suggested that all supposed ulcers of the stomach should be resected.

The therapeutic test of the effect of medical treatment is of great importance. If the symptoms are not completely relieved, and if blood has not ceased to appear in the gastric contents or feces, and if the crater of the ulcer has not diminished considerably in size and depth during three weeks of adequate medical treatment, operation should be done. If under continued medical treatment the supposed ulcer fails to heal completely, operation is also indicated.

The inadequacy of our methods of detecting cancer of the stomach

in an early and curable stage is shown by the fact that the disease is usually so advanced when exploration is done that resection is possible only in from 15 to 20 per cent of patients. The others are hopelessly incurable when they first consult their physician.

Epithelioma of the skin: Epithelioma of the skin is the second most frequent type of cancer in the male, and the fourth most frequent type in women.

Leaving aside the rare melanomas, which are so uncommon that they do not make much of an impression on data relating to skin cancer as a whole, it is fair to say that this is a kind of cancer that is so easily diagnosed and so easily controllable by good treatment that few deaths from it should occur. Unfortunately, we are far from attaining this ideal.

Patients, of course, often neglect skin cancer until it is well advanced, but we must also admit that physicians not infrequently fail to biopsy every suspicious induration or ulcer of the skin, and thus miss the chance of detecting the disease early. If this simple rule of biopsying every suspicious lesion were only followed, we would at once make a great advance in the control of skin epithelioma. It requires a certain degree of experience to distinguish senile keratoses and other benign lesions from epithelioma, but the physician who lacks this experience can perfectly well overcome his handicap by taking a biopsy. This is a simple office procedure, best done with a small, sharp knife after injection of a little novocaine adjacent to the lesion. Biopsy does no harm, and it has the great advantage of clearly establishing the nature of the disease so that appropriate treatment can be planned.

An exception to this rule is, of course, in lesions which are so small that it is convenient to excise them for biopsy in their entirety, together with an adequate margin of adjacent tissue. This implies an excision extending at least 5 mm. wide of the margin of the lesion on every side.

We feel that it is wrong to treat lesions of the skin of questionable nature by fulguration or by radiation without biopsy. If the lesion is an epithelioma, the treatment may not be radical enough. If it is benign, the treatment is needlessly drastic.

There is a great advantage in lesions of the skin, as elsewhere, in knowing surely and exactly the nature of the neoplasm. The habit of mind that insists on securing this information is more important than anything else in determining early diagnosis as well as good treatment.

Carcinoma of the uterus: Cancer of the uterus is, of course, one of the commonest forms of cancer in women. The cervix is affected about three times as frequently as the corpus.

Carcinoma of the corpus usually occurs after the menopause, when any uterine bleeding is a very suspicious sign and is an absolute indication for dilatation and curettage, to rule out carcinoma. In women who have not reached the menopause, irregular bleeding or spotting between periods, or excessive bleeding should also suggest the possibility of carcinoma of the corpus. A thin malodorous discharge is sometimes present. Dilatation and curettage are indicated if these symptoms persist.

In carcinoma of the cervix, vaginal discharge or abnormal bleeding are the usual symptoms. Inspection will usually reveal a suspicious erosion or fungating tumor of the cervix, and the diagnosis is easily made by taking a small biopsy with a simple biting forceps. When the disease is very early, and occupies only a small superficial area on the surface of the cervix, or when the lesion is hidden within the cervical canal, its detection may be difficult.

It is probably true that the only recent advance in the early diagnosis of cancer that has been made is in relation to epithelioma of the cervix. I do not refer, as you might think, to the Papanicolaou smear method of diagnosis, but rather to the discovery of the significance of the lesion which has come to be known as *carcinoma in situ*. It was about fifteen years ago that alert gynecological pathologists in several different clinics began to make the microscopical diagnosis of carcinoma in situ in the cervix. In this lesion the epithelium is thickened, but there is no downgrowth or invasion of the underlying stroma. The individual proliferating cells however, are hyperchromatic, vary abnormally in size and shape, and have all the characteristics of cancer cells. When these lesions first came to the attention of gynecologists, there was endless discussion as to whether or not they were malignant or benign. Today, because of the careful follow-up of patients with these lesions, and because of exhaustive microscopical studies of the lesions, it seems clear that carcinoma in situ in the cervix may be the initial phase of the development of ordinary cervix cancer. It probably exists as carcinoma in situ for a long time before it evolves to become infiltrating epithelioma. These facts have been established largely by work in the Women's Free Hospital in Boston, by Young, and in the Gynecological Clinic at Johns Hopkins by Te Linde.[3] In both Young's and Te Linde's series of

cases of carcinoma in situ, the average age of the patients was about thirty-five years, while the average age of fully developed carcinoma of the cervix was forty-eight. Both Young and Te Linde followed several patients with carcinoma in situ in which no treatment was given, and proved that the lesion eventually evolved into typical infiltrating carcinoma of the cervix. In both Young's and Te Linde's series, many of the patients who had carcinoma in situ were also found to have fully developed infiltrating carcinoma in other portions of the cervix when the uterus was removed and carefully studied.

Young has shown with beautiful kodachrome photographs that carcinoma in situ may be present in an apparently innocuous, simple erosion of the cervix, and that a faint spotty redness of the cervical mucosa is sometimes the only sign of its presence. In the great majority of cervices in which it was detected, the examiner had no suspicion that it was present. It was discovered only because Young and his colleagues biopsied almost every cervix that they examined. They used the Schiller test to indicate areas of abnormal epithelium, noted these with care, and took a biopsy from each with a biting forceps.

With this method of studying the cervix, namely, staining it with Gram's iodine and biopsying the suspicious areas, it would seem that it might be possible, if the examination were repeated at yearly intervals, to detect most carcinomas of the cervix while the disease is in a very early and easily curable stage. If this is true, the method offers a way of controlling cancer in the cervix which would make the disease as easily controllable, as, for instance, cancer of the skin.

We must, of course, also speak of the Papanicolaou smear test. The fact has been well established that these smears will often reveal carcinoma in the cervix when it is hidden from sight within the cervical canal, or when it is masked by an apparently innocuous erosion. In a series of 8,636 women in whom Papanicolaou smears were done, Jones and her associates reported finding nineteen carcinomas of the cervix which were not suspected clinically.

In Young's experience, however, the Papanicolaou smear was negative in about 30 per cent of the cases of carcinoma in situ which he discovered by routine biopsy. If the smear method had alone been relied upon, the disease in these women would have been missed. It is also well established that the smear method sometimes gives false positives. It would therefore seem that biopsy is a more reliable method of detecting

carcinoma in situ. At least for the present, it is more important to encourage routine biopsy than routine Papanicolaou smear. Finally, the microscopical interpretation of the Papanicolaou smear is more difficult than the interpretation of biopsy specimens, and few pathologists are at present qualified to interpret them.

Carcinoma of the breast: Cancer of the breast is twice as common as any other form of cancer. One woman out of twenty-five, according to our New York State data, will develop cancer of the breast some time during her life. This startling figure has recently been confirmed by morbidity data from Connecticut.[4] If he is to detect cancer of the breast successfully, a physician needs time in which to examine his patient and a good light in which to study the contour of the breasts. As carcinoma cells grow in the breast, they stimulate the proliferation of fibroblasts, not only in the tumor, but in the surrounding breast tissue. As the fibroblasts age, they contract, and through their connection with the fibrous septa of the breast which reach the overlying skin, as well as the underlying pectoral fascia, a whole series of retraction signs are produced. If I had time, I should like to illustrate these for you, but lacking that, you may see them illustrated, if you wish, in a forth-coming paper in the *Journal of the American Medical Association.* These retraction signs not only include the simple dimple over the tumor, but changes in the contour of the breast, elevation of the breast as a whole, distortion of the areola, deviation of the axis in which the nipple points, and flattening or retraction of the nipple. Bleeding from the nipple is only very infrequently a sign of carcinoma. It is usually caused by an intraductal papilloma. These papillomas, of course, must be excised and the possibility of carcinoma ruled out.

Any erosion of the nipple, no matter how small, is usually a sign of the Paget's type of breast carcinoma. This is merely a special type of breast cancer in which the carcinoma cells grow along the ducts from the primary tumor in the depths of the breast to reach the surface of the nipple. Every erosion of the nipple should be biopsied to exclude Paget's disease. When the diagnosis is confirmed, radical mastectomy should of course be done, just as for every other type of breast carcinoma.

There are so many benign lesions which closely simulate the clinical picture of breast carcinoma that biopsy often has to be done. Fat necrosis, the so-called sclerosing adenosis, and many other lesions produce

signs which may be indistinguishable from breast carcinoma.

Dr. Stout and I, at the College of Physicians and Surgeons, believe that incision biopsy is the best method. Through a small incision directly over the tumor, with careful hemostasis so that the lesion is well seen, we excise a tiny wedge of tissue from the surface of the tumor. The wedge need not be more than 3-4 mm. in diameter. This is sufficient for the preparation of a frozen section which gives us, almost without fail, a sure and certain diagnosis. In rare instances the frozen section is not decisive and we have to wait twenty-four hours for a paraffin section.

This kind of biopsy, of course, requires hospitalization of the patient and preparation for a radical mastectomy, should it be necessary. All this is desirable because thus both patient and surgeon are fully prepared for whatever may be required.

We disapprove of the aspiration method of biopsy for several reasons: In the first place, it is rough. Plunging a large bore needle several times into a firm carcinoma requires a good deal of force, which, we fear, may favor metastasis. Our first requisite in dealing with carcinoma is gentleness. Some time during the natural history of many breast carcinomas an embolus gets loose into the general blood or lymph circulation and hope of cure is gone. We do our best to avoid being an agent in this process.

Our second objection to aspiration biopsy is that it does not provide satisfactory microscopical evidence. The microscopical differential diagnosis of some of these breast lesions is very difficult, and the pathologist has a much better chance when he has a good sized section which shows the architecture of the lesion, rather than a smear showing only a few cells.

A third objection to aspiration biopsy is that the diagnostician cannot be sure that his needle is in the carcinoma. If he gets only nearby tissue cells in his needle, he may get a negative report and send his patient away with an undiagnosed carcinoma.

There are no new advances in the diagnosis of cancer of the breast, but we have yet a long way to go in utilizing to their fullest extent our present knowledge and proved methods of careful clinical and microscopical study of the breast.

Cancer Detection Clinics: A new development in the diagnosis of cancer is the cancer detection clinic. Since Dr. L'Esperance first organized a clinic of this kind at the New York City Infirmary in 1937, some

500 cancer detection clinics have sprung up in this country. The public interest has been whipped up by the propaganda of the cancer societies for these clinics, and the response from the public has been so marked that some of the cancer detection clinics are booked up with appointments for many months in advance. The aim in the cancer detection clinics is, of course, the diagnosis of unsuspected and symptomless cancer. Many of those who apply for examination, however, have symptoms referable to a specific organ or system. They have had their symptoms for some time, but fear or negligence has prevented them from consulting anyone. The cancer propaganda crystallizes their fear, and they rush off to the cancer detection clinic. We must, of course, recognize that the cancer propaganda is the immediate factor in making them seek medical care.

The point to be argued is not whether we favor propaganda urging people with or without symptoms to have physical examinations aimed at detecting disease, including cancer. We are of course in favor of this kind of preventative medicine. The question is rather, who ought to perform these examinations—local physicians or the staffs of cancer detection clinics. This is a complex question which must be considered from the viewpoint of what is best for the efficient organization of the practice of medicine as a whole, as well as from the viewpoint of which is the most efficient method of diagnosing cancer.

In considering whether local physicians can do as good a job of diagnosing cancer as the cancer detection clinics, it is important to divide cancers into two classes, the *accessible* and the *inaccessible* ones.

The first group includes, for example, cancers of the breast, cervix of the uterus, the skin, the prostate, the rectum, the lip and the buccal cavity. The diagnostic procedures required for the detection of these forms of cancer are relatively simple. They can be carried out in a physician's office and are certainly within the scope of any properly trained physician. The inaccessible forms of cancer include, among others, cancers of the stomach, colon, lung, pancreas, and ovary. The detection of these types of cancer is often exceedingly difficult, and indeed is impossible in many cases. Complex and expensive laboratory and operative procedures are required, such as gastrointestinal roentgen-ray study and bronchoscopy. These are, of course, not ordinarily available in doctors' offices. The local physician has to refer his patient to a hospital or special diagnostic laboratory for help in searching for these inaccessible

forms of cancer.

But what has been the achievement of the cancer detection clinics with these *inaccessible* forms of cancer? I have carefully studied the available reports from cancer detection clinics, and I find no evidence that they have had any significant degree of success in diagnosing the inaccessible forms of cancer. Dr. L'Esperance[5] reported that forty-eight cancers were found among 4,105 new patients examined during 1944 and 1945 in the Strang Cancer Prevention Clinic. Nineteen of these cancers were in the skin, nine in the breast, and six in the cervix. Fourteen others were listed as miscellaneous.

In five cancer detection clinics sponsored by the International Cancer Research Foundation in Philadelphia,[6] 5,279 women and 877 men were examined between 1944 and 1946. Cancer was found in five of the men; three having carcinoma of the prostate, one chondrosarcoma of the ilium and one carcinoma of the lung. Nineteen of the women were found to have cancer; five had carcinoma of the breast, four carcinoma of the cervix, three carcinoma of the fundus of the uterus, three epithelioma of the skin, one melanoma of the skin, one carcinoma of the gall bladder, one abdominal carcinomatosis, and one carcinoma of the skin.

It will be noted at once that neither of these reports claims the discovery of a single case of carcinoma of the stomach or colon. The reason, of course, is simply that examination has not included roentgen-ray studies. They would be too expensive for any cancer detection clinic to attempt routinely. Yet these are the most important types of cancer in which the cancer detection clinic might be able to offer the patient something that the general practitioner could not.

In our own hospital, Drs. Swenson, St. John and Harvey[7] have recently studied the frequency of symptomless gastric cancer in presumably well people. Dr. Swenson examined a total of 2,432 symptomless patients, over the age of fifty, fluoroscopically. His method was to do a rapid fluoroscopic examination without taking any films. In this way, with the help of two assistants and a stenographer to handle the patients, it was possible for him to examine as many as forty patients an hour. Three patients were found to have malignant gastric tumors, two of which were carcinomas and one a lymphosarcoma. The two carcinomas which were found had not metastasized, and resection was done with a good prognosis.

From this evidence it would appear that roentgen-ray studies would reveal at least one unsuspected carcinoma of the stomach in each thousand patients examined. When we face the hard fact of whether or no society is willing to assume the cost of such an undertaking, we must pause and estimate how much a human life is worth in dollars and cents. At our ward rates of $10.00 for a gastrointestinal series, detecting a single gastric carcinoma would cost $10,000. At our private patient rates of $60.00, it would cost $60,000. Assuming that the actual cost lies somewhere between these two figures and is perhaps $30,000, it is doubtful that the method is practical. Until some more economical method of detecting gastrointestinal cancer is discovered, the Cancer Detection Clinics are as helpless as the local physician.

While Cancer Detection Clinics have no advantage in the diagnosis of the inaccessible forms of cancer, they present a serious disadvantage from the viewpoint of the efficient organization of medicine as a whole. The propaganda for the Cancer Detection Clinics infers that practicing physicians are not capable of diagnosing cancer, and undermines the confidence of the layman in his local physician. This is unfortunate, for the diagnosis of disease in general is the responsibility of the general practitioner. Cancer is only one of the great diseases. We cannot contemplate taking away from the general practitioner his role in diagnosing it, or at least in putting his patient on the road to diagnosis. To do so would upset the whole balance of medical practice. If we carried out the principle of providing special facilities for the diagnosis of each one of the great diseases, we would entirely disrupt the practice of medicine. We would have clinics for the detection of heart disease, arthritis, cancer, diabetes, and so on, ad infinitum, and patients would rush from one clinic to another without any guidance. The waste of time and energy on the part of both physicians and patients would be beyond calculation. The general problem of the diagnosis of disease must and should remain in the hands of the well-trained general practitioner and internist. He should be the first to be consulted, and it is his duty to guide the patient to specialists if they are needed to carry out special diagnostic procedures or treatment.

To sum up the role of cancer detection clinics, we recognize the fact that the accessible types of cancer will be diagnosed in them if patients are solicited by the propaganda methods now widely used. We believe, however, that this is a task within the capabilities of the general

practitioner and internist and that the cause of good medicine in the broadest sense of the word is better served by urging patients to go to their local doctor than to go to special cancer detection clinics. He should be perfectly capable of doing a careful general physical examination and of detecting the accessible cancers. The inaccessible types of cancer, such as cancer of the stomach and colon, can be diagnosed only by expensive and highly technical methods. The cancer detection clinic can do no better for them than the local doctor. We must face the fact that we lack satisfactory methods for diagnosing inaccessible types of cancer. We should not, moreover, attempt to conceal this fact from laymen. We need the full understanding and sympathy of the public in whatever we attempt to do. These are the reasons why we have not opened a cancer detection clinic at the Presbyterian Hospital.

There is one provision that we must make when we reject the idea of the cancer detection clinic. It is that opportunities for the continued education in cancer diagnosis of the physicians now engaged in the practice of medicine be made available. Free post-graduate courses must be provided by the medical schools and hospitals where the general practitioner can learn the new diagnostic methods, such as those for carcinoma of the cervix. In this way the general practitioner can keep abreast of medical progress and offer his patients the best chance for early diagnosis.

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THE SURGICAL TREATMENT OF CANCER OF THE CERVIX UTERI*

(A Radical Operation for Cancer of the Cervix)

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CARCINOMA of the cervix is a relatively superficial lesion and, therefore, should be detectable early in its evolution. Measures for local destruction of these growths should prove highly effective in the early stages. The problem of propaganda among the laity leading to systematic examination of large groups of asymptomatic patients to detect early carcinomas of the cervix is a vital one but is beyond the scope of this discussion.

In the past three decades irradiation therapy has achieved a predominant position in the treatment of cervical cancer in this country, Canada, South America, England and most countries on the continent of Europe. It is generally held that most patients could be cured of carcinoma of the cervix by irradiation therapy properly conducted if these patients could be first seen in the earliest stages of the disease. The fact remains that the majority of patients when first seen, do not present the earliest stages of the disease and this situation is not likely to change very appreciably in the next few decades.

A review of the results achieved at the Memorial Hospital in the treatment of cancer of the cervix by irradiation from 1934 to 1941, reveals a more or less static situation in that about 28 per cent of all patients, year after year, were afforded a five year survival.[1]

Therefore, since the majority of patients developing cancer of the cervix continue to die of this disease, it follows that some consideration might be given to other forms of therapy. The only other form of therapy of proven efficacy is surgery. The objection might be raised

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that this has been tried and found wanting. In answer to this objection it may be pointed out that the surgery that has been tried was of a previous era and that the surgery of the present day has not been systematically exploited in the treatment of cervical cancer. It follows, therefore, that the position of modern surgery in relation to the problem of cervical cancer might be redefined at this time and this is discussed under several headings as follows:

1) *The natural course of carcinoma of the cervix.* This neoplasm, in its earlier stages, is strictly a local lesion. It spreads first by lymph channels to the parametrial nodes and nodes of the lateral pelvic wall and by direct extension to the vaginal vault, later producing discrete vaginal metastases. Finally, there is direct spread into bladder and rectal colon, metastases occur beyond the pelvis in periaortic nodes, liver, lungs, and bones. A feature to emphasize is the fact that in general cervical cancer does not rapidly spread to distal areas but apparently remains localized for relatively long periods. This is well illustrated by the sixty-five necropsy protocols from the Department of Pathology of the Memorial Hospital of patients dying with cervical cancer; 50 per cent of these had no gross evidence of the disease beyond the pelvis at death. They had succumbed from uremia, due to compression of the ureters, or from infection. Studies from other institutions have shown similar findings.[2]

Thus, carcinoma of the cervix is a lesion which remains relatively localized for prolonged periods; is not, as are some forms of lymphoblastoma, a systemic disease from the onset and does not, as does carcinoma of the stomach or pancreas, present distant metastases in the large majority of instances at the time the clinician first encounters the disease. Therefore, it would appear to be a lesion that is favorable for surgical attack.

2) *The operation for wide resection of carcinoma of the cervix.* The so-called Wertheim operation represented what was regarded to be the maximal of radical surgical attack upon cervical cancer in the early decades of this century. In principle, it consists of resection of the uterus, upper vagina and parametria. The operation as can be witnessed to-day in the Viennese gynecological clinics is a radical supravaginal panhysterectomy with limited parametrial excisions and does not include excision of the paravaginal tissues nor the lymph nodes along the external iliac and hypogastric vessels or obturator fossae.

Macroscopically involved nodes along the external iliac or hypogastric vessels are not systematically resected 'en bloc' with the uterus and parametria. A study of the illustrations accompanying the original article published by Wertheim in 1900, shows the variation in extent of the resections.[3] In some, just the uteri, adnexae and limited portions of broad ligaments were removed. In others, more of the parametria was resected, with a limited segment of ureter in certain instances.

The illustrations published in several American and foreign texts of the Wertheim operation show more or less the same procedure. In one important point, there is also a general similarity of description and that is that the lymph nodes from about the great pelvic vessels are to be excised *after* the uterus and adnexae are removed in some instances or are to be excised as individual nodes or groups of nodes. In Taussig's inguinal adenectomy, an adjunct to irradiation therapy of the primary growth in the cervix, the nodes are likewise resected individually or in small groups.[4] While such resections, as have been demonstrated, have been effective in permanent control of the disease in some cases, they do not conform to the basic principle of resection 'en bloc', i.e., excision of primary growth, affected organ, and adjacent lymphatics with surrounding tissues.

The English surgeon, Bonney, who throughout the years persistently advocated surgical treatment for cervical cancer, is often credited with being the most radical operator of his time in this field. In 1935, he described and illustrated his operation for American gynecologists.[5] The essential features are a radical panhysterectomy with parametrial excision performed after incision and opening of the broad ligaments. Much of the upper portion of the vagina is removed. The ureters are exposed from about the level of the origin of the uterine artery to the bladder. After the uterus and upper vagina are excised the question of pelvic lymph node resection is considered. Those along the external iliac vein are removed together with the hypogastric artery, but in early cases only the lymph nodes themselves are to be removed. As another and completely independent step, the areolar tissues and nodes in the obturator fossae are removed, sparing the obturator nerve. At the close of the operation a large flap of peritoneum has been spared in the anterior half of the pelvis and this approximated to lateral peritoneal flaps and to sigmoid, permits of complete peritonealization of the pelvis as a final step in the procedure.

The operation which has been planned and is being carried out at present at the Memorial Hospital for radical excision of carcinoma of the cervix and adjacent lymph node groups is as follows:

(a) Low mid-line incision extending to about 3 to 4 cm. above umbilicus. Palpation of liver, pancreas and periaortic region to ascertain absence of metastases.

(b) Usual retraction of bowels out of pelvis and patient placed in Trendelenberg position.

(c) The right infundibulo-ovarian ligament with vessels is divided. From this point upward the posterior parietal peritoneum is incised to over the bifurcation of the aorta. Areolar tissue and lymph nodes are dissected from above downward along the right common iliac vessels, including nodes and areolar tissue about the bifurcation of the aorta.

(d) The peritoneum over the external iliac artery is divided down to the round ligament which is transected between ligatures just as it emerges from within the abdominal wall. This exposes the right retroperitoneal pelvic spaces. The nodes and areolar tissues from above the external iliac vessels are dissected and wiped or pushed medially. By progressive dissection the areolar tissues and nodes in the deep right pelvic spaces and in the obturator fossa are mobilized and packed mesially. (The obturator nerve is spared.) The origin of the uterine artery is transected between ligatures as it arises from the hypogastric artery; several vesical and vaginal branches may be similarly divided. The large uterine veins as they reach the hypogastric vein are also doubly ligated and divided.

(e) By means of digital, gauze and instrument dissection, the fascia over the levator ani muscles and the arcus tendineus are exposed and "swept clean" of areolar tissues in the depths of the space created by the dissection. The right paravaginal tissues are likewise swept mesially against the right vaginal wall.

(f) The right ureter is now identified at the level of the brim of the pelvis and is freed progressively in the loosened areolar tissue, downward toward the bladder. Great care is exercised not to "shave" the tissues off the ureter completely but a certain amount of periureteral tissue is preserved in order to insure its blood supply. In freeing the lowest segment of ureter, parametrial tissue above it is divided and brought downward underneath it and mesially to preserve its attachments to the remainder of the broad ligament. Perivesical fat on the

posterior and infero-lateral aspects of the bladder is also stripped in continuity with the adjacent broad ligament.

(g) The peritoneal reflection from bladder onto cervix is divided near the midline and by blunt dissection the bladder is elevated. This separation is carried downward for a considerable distance on the anterior vaginal wall.

(h) The steps outlined above (c to g inclusive) are now carried out on the left side, the operator changing his position from the left side of the patient to her right side. Because of the loop of sigmoid colon and its mesentery, exposure of the upper left common iliac vessels is not always easily performed.

(i) The uterus and appended tissues can now be moved from side to side and this facilitates transection of the utero-sacral ligaments at a point lateral to the lower pelvic colon.

(j) The peritoneal fold between uterus and pelvic colon is now completely divided and the colon separated from the vagina. During this step the plane of dissection tends to be much nearer the colon than the vagina. By continuation of the dissection the pelvic colon is liberated almost to the end of the posterior vaginal wall.

(k) The vagina is then transected, as low as possible, the edges of the remaining cuff being secured with hemostats. The specimen is removed. Because almost all of the vagina is removed, the rim of the remaining cuff is deeply placed in the pelvis and its partial closure with one or two interrupted sutures is effected with some difficulty. A hard rubber tube is pushed downward out of the vagina to serve as a drain. Soft rubber drains may also be placed in each side of the pelvis and the lower ends pushed out of the vagina or brought out through the lower angle of the abdominal wound.

(l) Because of the extent of the dissection which literally includes all of the pelvic peritoneum except that lying over the dome of the urinary bladder, peritonealization is not possible nor is it necessary.

(m) Closure of the abdominal wound in layers with soft rubber drains in the lower angle leading to each side of the pelvis.

The operation accomplishes a complete removal of the uterus and adnexae, the entire broad ligaments and paravaginal tissues, the pelvic lymph nodes, lymph channels and areolar tissues about the common iliac, external iliac and hypogastric vessels, the lymph nodes and areolar tissues in the obturator fossae, the areolar tissues on the posterior and

Stage of Disease	*Number of Patients Operated Upon*	*Surgical Mortality*
1. Very advanced; extension beyond pelvis. Exploratory operation with or without bowel resection for intestinal obstruction	6	0
2. League of Nations Stage I. Schauta operation	6	0
3. Radical pan-hysterectomy with pelvic node dissection for cancer of cervix in L. of N. Stages I, II, and III	37	0
4. Radical operation with excision of portions or all of bladder or with portion of rectal colon for disease in L. of N. Stage III	12	1 (8.3%)
5. Complete excision of all pelvic viscera with ureteral implantations into colon and colostomy. Disease in L. of N. Stage III or IV	12	3 (25%)
Total	73	4 (5.5%)
Exclusive of category 5 (far advanced cervical cancer not controlled by previous irradiation therapy and/or conservative operation)	61 patients	1 death (surg. mort 1.6%)

inferior lateral surfaces of the bladder wall. And, finally, practically the entire visceral and parietal peritoneum with its subjacent areolar tissues. The latter feature is important because of the rich lymphatic channels which are here present and in free anastomosis with the lymph channels and nodes in the parametria and along the great vessels of the lateral pelvic walls.

3) *Lymph Node Metastases:* It has been stated that once epidermoid carcinoma of cervix has metastasized to lymph nodes in the parametria or lateral pelvic walls, the condition is beyond hope of cure by irradiation because metastatic carcinoma in lymph nodes can not be destroyed by irradiation. While the chances for cure in this stage by irradiation are not great, I would not agree with the hopelessness of the situation from the radiotherapeutic standpoint if the statistics reported for radiotherapy are correct. Certainly all of the five year cures in Stages I., II. and III. can not have been patients without lymph node metastases. Therefore, in some instances of lymph node metastases the disease has probably been controlled by irradiation.

If one compares the clinical findings in any series of patients with the pathological study of the specimen, it becomes apparent that frequently a small primary growth has given rise to one or two metastatic nodes which are not clinically appreciable. Thus all cases classified as League of Nations Type I. or II. (without parametrial extension) can not be strictly in this group, etc.

In the surgical operation described above, the systematic excision of practically all parametrial and lateral pelvic wall nodes is carried out. This, it would appear, has a distinct advantage over a radiotherapeutic procedure, for conceivably the group of patients in whom there are one, two or a few node metastases without further extension of disease, might have a greater opportunity for cure following 'en bloc' resection than with only irradiation.

(4) *Operability:* In the previous controversy of irradiation therapy versus surgery in the treatment of cervical carcinoma, it was stated that the surgeons exercised considerable selection of their patients. This was undoubtedly true and any degree of fixation of the uterus or even appreciable parametrial involvement often led to a classification as "inoperable." Wertheim and the earlier operators did not hesitate to operate upon some patients with parametrial involvement. Bonney repeatedly declared that a number of so-called Type III. cases were operable and stated that his operability was 63 per cent. Meigs, on the other hand, was interested in a specific phase of the problem, namely, to demonstrate that in selected patients with small lesions, situations in which surgical therapy should prove highly effective, the argument of surgical risk could not be raised as a deterent to operation. He has amply proved his point and states that 10 to 15 per cent of all cervical cancers are operable. He is, of course, referring to surgery as the treatment of choice in the selected patients with early lesions (League of Nations Type I. and II.) which he estimates constitutes 10 to 15 per cent of the patients first seen in consultation.[6]

Obviously the next step in the exploitation of a surgical attack upon cervical cancer is to ascertain if selectivity may be reduced to a minimal degree consistent with good surgical judgment. At Memorial Hospital, at present, a minimum of selection is exercised. Since September 1947, every patient with cancer of the cervix is evaluated as a surgical problem. If there is clinical or roentgenologic evidence of spread beyond the pelvis (inguinal node involvement is not considered extrapelvic

spread) the situation is, of course, regarded as inoperable. Between September 15, 1947, and April 24, 1948, there have been 81 patients with carcinoma of the cervix, all evaluated as surgical problems. In 73, operation was performed. Thus the explorability rate was 90 per cent. Operation was not carried out in 8 cases because of clinical evidence of extra-pelvic spread in 3 instances; in 2 instances of irradiation failure poor physical condition precluded operation and irradiation therapy was again instituted in attempt at further palliation; in 1 instance the general condition was too poor for any treatment and the disease was in its terminal stages; in 2 instances the patients preferred radiation therapy to operation. Among the 73 operated cases, exploratory laparotomy only was carried out in 6 instances. In 67 patients a radical procedure was performed. Thus the operability rate was 82.7 per cent. It is not implied that operability is synonymous with curability since many of these radical procedures were undertaken for palliative purposes only, a cure being out of the question.

The series referred to is not a large one but in view of the fact that it represents as far as possible an *unselected* group of patients; it is presented here in answer to the question so often raised that any surgical attack upon cancer of the cervix must of necessity be somewhat restrained because of the rather high degree of selection that it is anticipated that the surgeon will exercise.

It has been my experience that the so-called "frozen pelvis" is not necessarily indicative of carcinoma extending in solid sheets from the region of the cervix to the muscles of the lateral pelvic walls. The view from within the abdomen downward, as it were, is very frequently much more hopeful from the standpoint of circumventing the process surgically, than might be expected from bimanual vagino-rectal examination. A free plane of dissection can usually be found in the lateral spaces of the pelvis. In only one instance in this series have I been forced not to carry out excision because of invasion of the fascia over the levator ani muscles which afforded literally a "frozen pelvis."

5) *The question of surgical mortality:* It is the factor of surgical mortality that exerted a great influence in the general adoption of irradiation therapy for cancer of the cervix some years ago. Text books of gynecological surgery almost unanimously caution concerning the high mortality of the radical surgical attack upon cancer of the cervix. The mortality from all major surgical procedures for visceral cancer

was relatively high a few decades ago but by persistent efforts in many directions this has been very greatly reduced.

Bonney's mortality was approximately 15 per cent in 500 somewhat selected cases. Meigs[6] has shown that with the benefits of modern supportive therapy, the mortality in a series of 91 cases was nil (report published in 1947). However, Meigs' patients, it must be admitted, represent a rather highly selected group, namely, and to use his own words, "they were good risks, thin, young and with tumor involving not more than the complete cervix and part of the vaginal wall." Meigs' studies were conducted with a special objective, that is to demonstrate that in a group of patients with small lesions and in whom, therefore, surgical attack should prove highly effective, the mortality could be brought to such a low point that the factor of surgical risk could not be raised as a deterent to operation. This point he has very amply proved for the selected group.

In the series of 73 consecutive and unselected patients with cervical cancer referred to in the previous section, the operative mortality was as follows:

The overall mortality in the series is 5.5 per cent. The mortality is confined to the group presenting the most advanced local stages of the disease. These patients had all had one to several attempts at irradiation therapy with or without some form of local operation. In the group of 49 patients who had the radical operation and in 12 instances of which there were additional resection of viscera, the mortality was 2.0 per cent.

(6) *The problem of recurrent and advanced cancer of the cervix. Palliation by radical surgery in advanced cancer of the cervix.*

Where repeated irradiation therapy with or without some form of conservative operation has failed to eradicate the disease, continued irradiation will offer little opportunity for palliation beyond perhaps a temporary restraint in the progress of the disease. If certain limits are exceeded, tissue necroses may develop which may prove as distressing to the patient as the advancing neoplasm itself. Since cancer of the cervix may be advanced locally and yet not have metastasized beyond the pelvis, radical excision may be envisaged. These operations have been carried out on a number of occasions and may be divided into four categories as follows:

(a) When the disease is apparently still localized to the cervix and upper vagina, a radical panhysterectomy with pelvic lymph node re-

section can still be performed.

(b) When there is local recurrence and invasion of the rectum, a complete excision of the vagina and uterus and invaded portion of the rectum is feasible with reconstitution of the rectum by end to end anastomosis.

(c) When the lesion has recurred and invaded the bladder, the uterus, vagina and entire bladder may be resected with bilateral ureteral implantations into the colon. When only one ureter and a portion of the bladder are involved, the invaded portions alone may be excised.

(d) When the bladder and rectum are both involved, the uterus, vagina, bladder and rectal colon can all be removed "en masse." Patients with such advanced disease can be rehabilitated to almost normal activities, at least for appreciable periods.

Patients who receive extensive resections for uncontrolled cervical cancer can hardly be expected to survive five years or more. The operations are carried out for palliative purposes only and sufficient time has now elapsed to convince me, at least, of their value in this respect. The only other alternative is increased sedation but this does not relieve the distress associated with fistulae and other discomforts due to the presence of large infected neoplastic masses.

In regard to the possibilities of palliation, therefore, surgery would seem to have something to offer after other and more conservative measures have been exploited to the maximal extent and the disease remains and is still progressing.

The combination of surgical and irradiation therapy. The large majority of cervical carcinomas exhibit immediate and appreciable to complete macroscopic regression following properly conducted irradiation therapy. It would appear for the present, at least, to be contrary to good judgment not to take advantage of this fact even in a program to re-evaluate the possibilities of surgery. A priori, it would seem that a radical operation carried out in the presence of a regressing neoplasm has advantages over one performed in the presence of a flowering growth. Furthermore, a number of cervical carcinomas form papillomatous masses that bleed easily and are heavily infected. Irradiation will reduce the size and vascularity of these growths and there is a subsidence of local infection. In all of the patients subjected to radical operation for cervical lesions that appear localized to the cervix and its immediate vicinity, intra-vaginal roentgen-ray therapy by means of special

cones is carried out. Three thousand to 3500 r measured in air are delivered to the cervix and in some instances to each parametrium. Where the lesion is more extensive and has not been previously irradiated, the usual pelvic cycles are administered. Operation is performed four to six weeks after the last treatment.

This combination of irradiation and surgery does not cloud the issue as to an improved method for the management of cervical cancer. An extensive experience in purely irradiation therapy of this lesion has been gleaned in many centers throughout the world in the past three decades. The important objective is not to decide which is the better treatment, irradiation alone or surgery alone. This is an academic question. The principal objective is to increase the incidence of cure among all patients who present themselves with carcinoma of the cervix and to devise ways and means of increasing effective palliation when cure is out of the question.

Discussion. I do not concur with the view that a planned program for the evaluation of a modern surgical approach to the problem of carcinoma of the cervix is an experiment in the usual sense of experimentation. This would imply that irradiation therapy has reached such a stage of proficiency that any other form of management is contrary to good judgment and the best interests of the patient. That irradiation therapy still leaves much to be desired in the face of the varied stages of the disease encountered in patients as they present themselves, is generally conceded. Therefore, a program in which radical surgery is the principal arm of attack might better be referred to as another approach to the problem.

Years of extensive experience are necessary to properly evaluate the benefits of surgical treatment for a relatively slowly progressing neoplasm. On the basis of the brief and limited experience that has been recorded above, no conclusions are now possible, and there can be no presumption to recommend alteration in the methods at present generally carried out for the treatment of cervical cancer. All that may be said is that this presentation has been a report of a type of clinical investigation in progress on the problem of cervical cancer.

Summary

1. For reasons enumerated, a statement of the position of modern radical surgery in relation to the treatment of cancer of the cervix is made.

II. A radical operation is described for excision of carcinomas of the cervix that have not involved bladder or rectum. This procedure would appear to be more extensive than hitherto carried out for this type of neoplasm. The 'en bloc' excision of uterus, most of vagina, parametria, areolar tissues and lymphatics of the lateral pelvic walls, and the removal of practically all the pelvic peritoneum except over the fundus of the bladder and on the pelvic colon and its mesenteries, is emphasized.

III. Procedures are mentioned for excision of involved viscera adjacent to the cervix in instances of advanced carcinomas of the cervix. These procedures are capable of affording a degree of palliation not possible by other known measures in the face of previous failure of irradiation with or without conservative operation in these patients.

IV. Data are presented to show that, thanks to modern supportive measures for the surgical patient, selection of patients for operation can be quite appreciably reduced in comparison to the selection exercised in the past, and, what is more important, surgical mortality can be kept at such a level that this can no longer be held as a major deterent to the surgical approach to the problem of cancer of the cervix.

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COMMUNICATION TO THE EDITOR

New York, September 14, 1948

Dr. Mahlon Ashford
The New York Academy of Medicine
2 East 103rd Street, New York 29, New York

Dear Doctor Ashford:

It has come to my attention that there is the possibility of misinterpretation of two statements in my article on the "Prophylaxis of Cancer" read before the 19th Graduate Fortnight of The New York Academy of Medicine, October 18, 1946 and as published in the BULLETIN of The New York Academy of Medicine in July, 1947. I wish to modify these statements and hope it will make my meaning crystal clear.

The first statement appearing on page 385 of the BULLETIN reads as follows:

> "The removal of all precancerous lesions of the skin will save many a life from cancer, as skin cancer is the easiest of all types to cure."

Please substitute the following as more clearly conveying my meaning:

> "*The early and proper treatment of malignant or suspicious skin lesions will save many lives, for skin cancer offers the greatest opportunity for cure.*"

The second statement I would like to modify appeared on page 386 of the BULLETIN and reads as follows:

> "Any one who has ever had even a single dose of low voltage x-ray to the skin is a possible candidate for subsequent skin cancer."

For this statement I wish to substitute the following:

> "*Under certain conditions and dosage, x-ray to the skin can produce skin cancer. Therefore this ray should never be used except by experts in this form of treatment. Well trained dermatologists using x-ray in the treatment of skin diseases are experts in this form of therapy.*

In order that there may be no misunderstandings of my meanings, I would appreciate it if this letter be given publication in the BULLETIN of The New York Academy of Medicine.

Very truly yours,

FRANK E. ADAIR